

RES MEDICA

Journal of the Royal Medical Society



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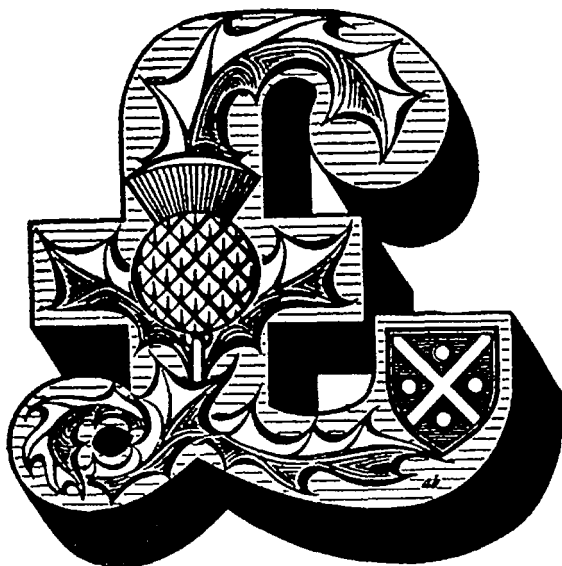
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THE JOURNAL OF
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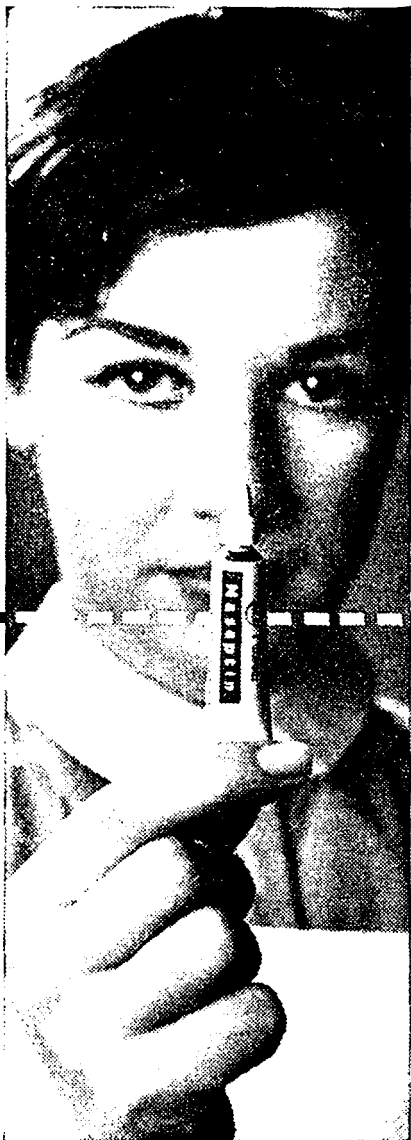
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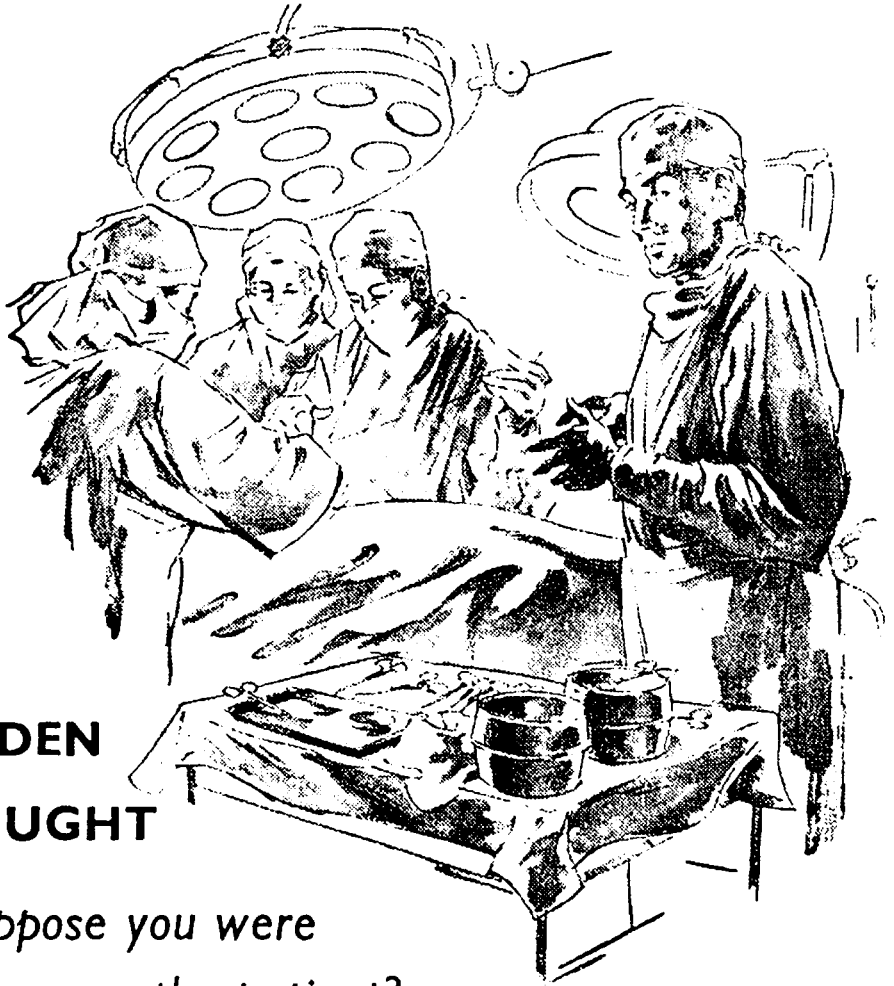
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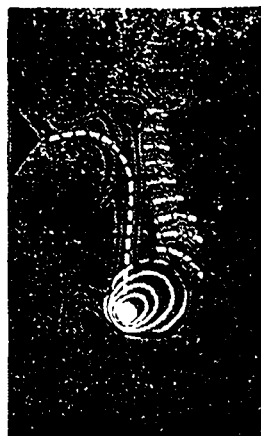
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BRAIN MECHANISMS AND SOCIAL PROBLEMS

BY W. RITCHIE RUSSELL

C.B.E., M.D.(Edin.), D.Sc.(Oxon.), F.R.C.P.(Edin. and Lond.)*
Director, Department of Neurology, United Oxford Hospitals

Based on an Address delivered to the Royal
Medical Society on 4th December 1959.

Knowledge with regard to the Central Nervous System (C.N.S.) is increasing so quickly that it is difficult to adjust one's ideas to the ever-changing scene. When we turn for help to the ideas of great thinkers in the past, it becomes apparent that these are now of limited importance for the simple reason that they were building castles with bricks which are now known to be inadequate. It seems desirable therefore that we should from time to time stand back and view the whole problem of how we use our brains or of how our brains use us.

The neurologist is constantly studying the effect of lesions of the C.N.S. on functions and behaviour, so that he is forced to consider the physiological mechanisms involved.

It was Hughlings Jackson who realised more than anyone in his time, how much may be learned by studying what he called dissolution of the various levels of the nervous system, but it is just as important to study the development during infancy and childhood of the patterns of behaviour. I think that the work of psycho-analysts is of the greatest importance in this regard, for they have shown how the features of an adult's behaviour can be traced back to the earliest reactions of that individual in infancy. This is so striking a phenomenon that those interested in education are paying more and more attention to the importance of the infant-parent relationship, for it is in infancy that the earliest seeds of future behaviour are sown. This all-important aspect of the development of behaviour patterns is becoming much easier to appreciate as a physiological matter than was possible even a few years ago.

I should like in the first place to stress what is really obvious, namely that nearly all our reactions are based on the repetition of previous responses. This affects all aspects of C.N.S. activity so that the way we learn to walk, speak, play or think becomes so strongly fixed that our friends know us by our posture or gesture, and our banker recognizes our signature as being something unique to us.

These same features of C.N.S. activity are apparent in the higher forms of activity, and we can often tell what our colleagues or friends are going to say in advance, for they react to the same situation each time in much the same way. I am not suggesting that we need be entirely controlled by habit, that is by repetitions, but the first tendency is always to do what was done before, and a special effort is needed to change the pattern. Some people make this effort to avoid getting in a rut more than others, and a few people make a special habit of reacting differently on each occasion, but this trait, though it adds much to the pleasure of social contacts, is in itself a repetition. Our so-called characters seem to be concerned with what particular type of repetition we favour.

* Dr Ritchie Russell is a former Senior President of the Society.

It is difficult to realize that the neuronal structure of the brain has been known about for little more than half a century. Before that it was not surprising that ancient philosophers paid little attention to the C.N.S., for the brain provides a very "Silent Service" which produces sensations referred mostly to other parts of the body. However, having discovered that we each possess about 10,000,000,000 neurones it is naturally important to study the behaviour of these separate units, and it is fair to say that the more we learn about them the more astonished must we become by the complexity of the mechanisms involved. At the same time it is disconcerting to learn that nerve cells, after the age of 20 years, probably disappear at the rate of about 50,000 a day.

I shall not attempt to explain what is known of the mixture of the physical and chemical which constitute neuronal activity, but it does seem important to emphasize that nerve cells are extremely active units, which discharge as an infinite variety of "strengths" and this is determined by the rate of discharge—a phenomenon which is associated with depolarization of the cell membrane. The rate of discharge may be anything up to 500 per second for some of the most active cells.

It seems probable that the brain cells are seldom waiting idly for something to do for even when we think they are idle, they are probably discharging at a slow rate and are exercising as it were, through the neuronal circuits they have formed. In this way the spontaneous repetition of activity in a particular direction strengthens the previously established neuronal connections, and probably provides a physiological explanation of the great strength of the repetition-systems which constitute our habits.

In order to study further the behaviour of separate cells, we have to turn to the brilliant researches of physiologists such as Eccles (1957), Granit (1955) and Charles Phillips (1956), for they have been able to record from individual cells in the spinal cord and brain and to analyse many aspects of their behaviour. In addition to the spontaneous activity which they have studied they have shown that the occurrence of central synaptic transmission is followed by a state of reduced threshold which facilitates a repetition of the same reaction. This is a most important matter, for it provides a physiological basis for the repetitive action which is such a vital feature of all C.N.S. activity. The exact mechanism of this encouragement of repetition is not very clear, but the change seems to take place in the synaptic terminals, and it seems to provide a physiological clue to the fact that repetition is one of the most striking features of all C.N.S. activity.

Now it is obvious that if all our nerve cells are discharging night and day throughout life, this constant activity provides much of what is needed to maintain various patterns of neuronal activity. This is probably the physiological basis of a capacity to repeat a skill such as writing, in our own inimitable way.

Further, the suggestion that the brain is always strengthening its patterns, provides some explanation of our remarkable capacity to remember, say, how to swim or ride a bicycle after many years of neglect of these skills. This I think is easier to understand if we imagine that the spontaneous activity of these neurones concerned with bicycling is to some extent practising bicycling throughout life *via* its spontaneous activity.

If this view is correct then the capacity to repeat seems to be a basis of remembering how to swim, and the physical changes relevant to this achievement are probably situated in the synaptic apparatus rather than the cell body; at least it is here that physiological observations have demonstrated a mechanism which would encourage repetitions to occur.

The next question is concerned with whether what we call the psycho-

logical forms of memory demand a separate physical explanation, or whether they can be explained as an elaboration of the mechanism involved in remembering how to swim.

It seems that there is much to suggest that both depend on similar mechanisms. Thus the study of organic amnesic states shows not only an incapacity to establish new memories, but an astonishing strength of certain remote memories which can have been of no special importance to the individual. I have been specially interested in recovery from concussion in which remote memories recover first so that a gradual shrinkage of the retrograde amnesia is often a remarkable feature (Russell, 1959).

It seems that certain remote memories strengthen themselves with the passage of time regardless of their importance to the individual while recent memories of the greatest importance are very vulnerable to the effects of concussion. These characteristics of remote and recent memories may to some extent be explained on the basis of constant neuronal activity strengthening memories automatically. In other words our memories may depend not on molecular changes within the nerve cells but on changes at the synaptic part of cell systems, and these changes are always being maintained by the active and spontaneous discharges of neurones.

On the other hand all severe head injuries after recovery demonstrate the phenomenon of retrograde amnesia, and this must surely mean that a repetitive system must operate some hundreds of times before it will withstand the paralysing effect of concussion. Retrograde amnesia often only covers a period of a few seconds but that is a long time for a neurone that may discharge at up to 500 times per second.

I would suggest therefore that these aspects of remembering are consistent with the mechanism I have just put forward.

There is another aspect of C.N.S. activity that must be given some consideration. It is obvious that our sense organs, especially our eyes, are bombarded continually with impulses which we never notice at all. Almost everything going to the brain seems to be automatically extinguished, but then of course the inhibitory system in the C.N.S. is probably even more important than that concerned with excitation. Psychologists have sometimes thought that everything seen is remembered except what we want to forget, but this approach is unacceptable in the light of current physiological knowledge. Recent work however suggests a previously unsuspected effect on peripheral thresholds of sense organs such as the retina which is exerted by the brain. The centrifugal effect on the sense organs seems to have the power to control peripheral thresholds to a remarkable degree.

In any event it is clear that some alerting system has to operate before the images on the retina are noticed at all. Whether they are suppressed before or after reaching the calcarine cortex is difficult to be sure of but it should be appreciated that the striate area is but a receiving station for the visual system. It is what happens beyond the calcarine area that is of such great interest and we may infer the presence of some simple features.

In the first place, as regards looking at things, the familiar must be distinguished from the unfamiliar. The familiar is often associated with a contented type of feeling response while the unfamiliar is potentially dangerous and may alert aggressive or fear responses. There is plenty of evidence to indicate that the hippocampal mechanism is very much concerned with both establishing a memory (visual in this example), and also in enabling a memory to re-arouse the feelings which were previously associated with the same thing. The recognition of the familiar seems to be a very fundamental aspect of all afferent mechanisms and seems to form an essential part of memory mechanisms.

The feeling of familiarity in temporal lobe fits is probably highly significant in this connection as also is the capacity of abnormal activity in temporal lobe lesions to lead to hallucinations of almost any of the senses. Hallucinations are presumably distorted memories and are sometimes concerned with memories from early childhood: these however may be mixed with more recently acquired images as in the case of a friend of mine, a consultant neurologist, who when ill with bulbar poliomyelitis had an hallucination of himself curled up in one of the brain stem nuclei!

The remarkable effects of excising both temporal lobes support this conception of the importance of the hippocampal system, (Scoville and Milner, 1957), for it evidently leads to loss of recent memory and indifference to sights and sounds which formerly caused emotional responses.

However we must turn to an even more primitive part of the brain in order to study the beginnings of behaviour patterns. Perhaps we might begin with the foetal opossums which about ten days after conception climb out of their mother's womb up her abdominal wall into her pouch where they remain for many weeks. When they make this remarkable trip their nervous system seems to consist of little more than a fifth nerve nucleus; the upper limbs consist of what amount to two hooks and the lower limb buds are hardly visible. The automatic movements of the head and upper limbs enable the mouth to find a rudimentary nipple in the pouch. The whole affair provides a wonderful example of the importance of the mouth and the trigeminal nerve in relation to the earliest reactions of the body.

From the point of view of behaviour patterns it is necessary to emphasize that all organisms facilitate reactions which seem to the organism to be desirable, and inhibit those which are harmful. This can be demonstrated in very primitive forms of life, and in animals which have a well-developed central nervous system it seems that the pituitary-hypothalamic system is responsible for these all-important aspects of development.

There have been many experiments of the electrical stimulation of these hypothalamic centres in mature animals, and very dramatic emotional responses have been demonstrated. The most astonishing development I think is that of Olds and Milner (1954) who implanted electrodes in a rat's brain in such a way that the animal could stimulate a certain area of his own brain by pushing a small lever. These workers found that from certain areas of the rhinencephalon forebrain and cephalic brain stem the animal would repeatedly stimulate his own brain over long periods of time to the exclusion of other activity, at rates of up to 8000 times an hour. The cingulate and hippocampal cortex also had some effect in this direction.

Here then we have abundant evidence of facilitating and inhibiting mechanisms which in the adult animal, and no doubt the human being also, are inexorably mixed up with the well-known feeling of fear, pleasure, anger, etc. We can but conclude that these powerful feelings tend to dictate the pattern of behaviour, and if we realise that all responses tend to repeat themselves with ever increasing constancy, we come to appreciate the overwhelming importance of the earliest feeling responses. Here we return to the same view that has been arrived at by psychoanalysts from a different approach.

It seems that the individual's ultimate capacity and behaviour depend so much on his earliest feeling responses that they become the most important steps in the development of the adult behaviour patterns. If this is a sound argument then the parent assumes an importance which is so great that his or her education becomes the most important aspect of national education!

Thus it seems reasonable to maintain that you might first decide what

you want your children to be like and then work out the optimum feeling response and keep encouraging it in relation to what you want.

Many studies of neglected children demonstrate the astonishing improvement in intelligence which results if the feeling environment is improved, and we all know the remarkable influence exerted by what we call "a good mother." The importance of early parental love is all too well recognized by social workers in preventing strong anti-social traits, for the infant's feeling reaction to his parent seems to establish to a large extent his future reaction to his fellow men.

Of special interest must be the probable effect of early influences on intelligence, for if this can be profoundly influenced by an early favourable feeling-response to acquiring new knowledge and a general wish to explore the unknown, then our whole national plan for education may prove to be partly misdirected. The family tradition of learning may yet prove to be the most important factor in acquiring intelligence. It is perhaps particularly unfortunate that the highly intelligent child from an uninterested home may have developed intelligence as a rebellion against his environment so that students with this background are most likely also to be anti-social in their behaviour.

I would like to suggest therefore that the modern educationalist should pay less attention to the avoidance-of-trauma aspect of psychology, and should engage in much research on the positive aspect of education from the earliest months of life. The fronto-hypothalamic system may have the last word as far as the individual's behaviour is concerned and the great emotional drive from this physiological mechanism has possibilities which have been little studied in the educational field.

We must also give full due and regard to the far-reaching value of group or tribe loyalties, traditions, religions, creeds and customs. These all introduce a regulating discipline into life which is obviously of the greatest importance.

As far as man is concerned the feeling response to his environment and his activities develops a highly complex mechanism for which the integrity of the prefrontal lobes seem to be important. This prefronto-hypothalamic mechanism seems to provide a highly developed elaboration of what begins in hypothalamic mechanisms, and this is therefore a vital anatomical region as far as the development of behaviour patterns are concerned. The development of these patterns occurs to a large extent during childhood and I suggested some years ago (Russell, 1948) that the integrity of this system is of special importance to the infant and young child, so much so that loss of the prefrontal lobes in infancy must make education impossible and also render very difficult the establishment of satisfactory behaviour patterns.

In adults on the other hand behaviour patterns and educational levels are already established, and it seems that for this reason we can do without the prefrontal lobes without necessarily any very noticeable change in our behaviour patterns. In adult life, however, if the frontal mechanism has to work very hard to control some strongly distorted behaviour pattern, then loss of frontal control may lead to the so-called frontal lobe syndrome in its florid form. A study of soldiers with frontal brain wounds led to the conclusion that the subsequent clinical picture depended largely on the type of previous personality (Jarvie, 1954).

I should like again to emphasize that from the physiological point of view the individual's behaviour pattern seems to be formed by the nature of his feeling responses to his environment, and the earliest aspect of this must be closely connected with the infant-mother relationship.

Young mothers of today are in general unaware of their very special

importance in education and it seems to me that in general they would benefit from some education in this direction.

It is worth while also to consider from the physiological point of view how to deal with the individual whose anti-social or psychopathic behaviour leads him to be a nuisance to the community.

From this point of view we would not expect much advantage from attempts to reform his attitude by education or argument. There is much more sense in a policy of introducing discipline of some kind which involves making it obviously no longer worth while to be unconventional or anti-social. This is the only type of reforming that is likely to succeed with psychopaths, and indeed disciplines seem to be advantageous to most forms of education.

Finally, may I point out that although it is fashionable nowadays to belittle traditional customs and religions, we must surely continue to support what has proved itself of value to the community. It may be impossible for the scientist to swallow much of what he is asked to believe, yet I feel that we should encourage any organization which concerns itself with improving standards of human behaviour.

On the other hand it seems important that ancient beliefs should be modified intelligently in the light of new knowledge, and it should be recognized that modern thought is much more attracted by action than by beliefs. Indeed new knowledge suggests that there are fresh fields for activity for those who devote their lives to problems of human welfare.

In conclusion, I hope that with these few remarks I have succeeded in showing that ideas regarding brain mechanisms must be considered in relation to problems facing mankind, and in particular that a more positive and physiological approach to the development of the individual's personal characteristics is a matter of considerable importance.

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PORTAL HYPERTENSION

By J. G. CLARK

Based on a Dissertation read before the Royal Medical Society on Friday, 15th January 1960.

Definition

Portal hypertension is a condition of chronically raised pressure in the portal venous system, giving rise to splenomegaly and the development of enlarged collateral venous channels connecting the portal and systemic circulatory systems.

Anatomy

Figure 1 illustrates the disposition of the main veins of the portal system, and indicates the chief sites at which this system communicates with the systemic veins. The presence of a Caput Medusae in cases of intrahepatic

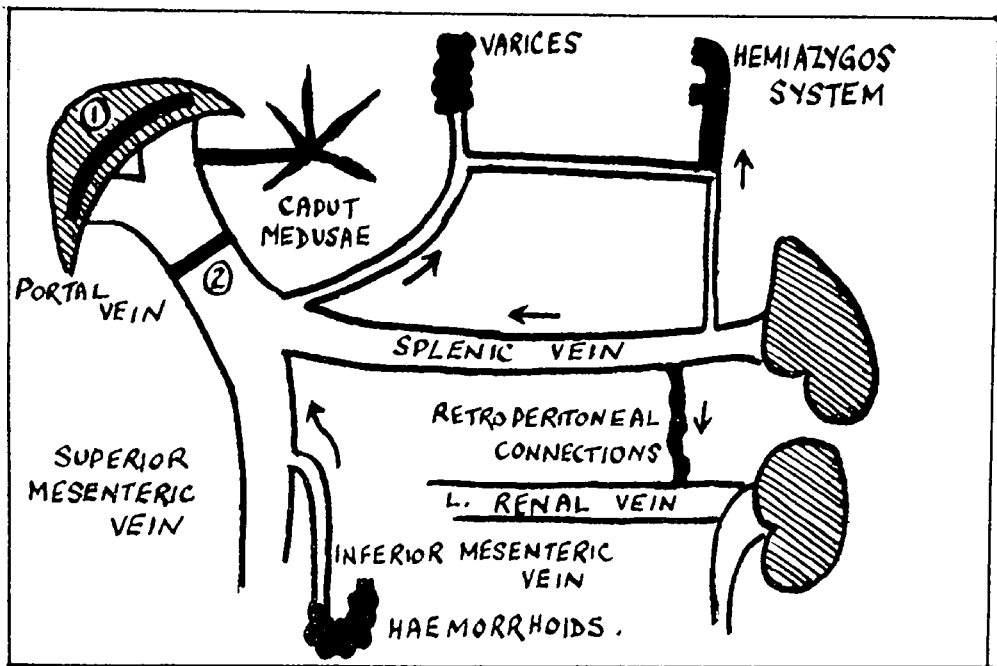


DIAGRAM OF PORTO-SYSTEMIC CONNECTIONS

- ① INTRAHEPATIC BLOCK
- ② EXTRAHEPATIC BLOCK.

Fig. 1

obstruction, and its absence in extrahepatic obstruction, is evident from the drawing. Not all of these sites are important clinically or diagnostically, but their total capacity causes a very considerable volume of blood to bypass

the liver and be released into the general circulation when the communications are enlarged.

The vascular structure of the liver is important, and I have illustrated this with a diagram (Figure 2) on which it is readily seen how easily inflammatory and fibrotic processes can cause obstruction of flow and therefore raised portal pressure. Understanding of this structure is fundamental to the comprehension of liver pathology, and the clinical conditions to which it can give rise.

Physiology

There is no justification for attempting to include here the ocean of hepatic physiology in the sea of portal hypertension, and I shall limit my remarks to three subjects.

Firstly, in the realm of biochemistry, *protein metabolism* is of greatest interest in this condition, but it will be more convenient to discuss that later on in connection with portal neuropathy.

Second, *blood flow*. The amount of blood reaching the liver is controlled by the sympathetic system operating in the gut. This variable input is dealt with in the hepatic vascular bed by a mechanism which is as yet ill-understood. It has been shown in rats that the area of liver bed in use at any one time is controlled by means of opening and closing of the peripheral parts of it. The mechanism by which this is perpetrated is not known, and the existence of porto-hepatic communications has been proposed by some workers and denied by others.

Total liver blood flow in a normal adult has been shown to be about 1600 ml./min.

Third, *portal pressure*. This can be measured in three ways:—

- (a) Canulation of an omental vein at operation.
- (b) Percutaneous splenic puncture.
- (c) Wedge manometry of hepatic venous radicals.

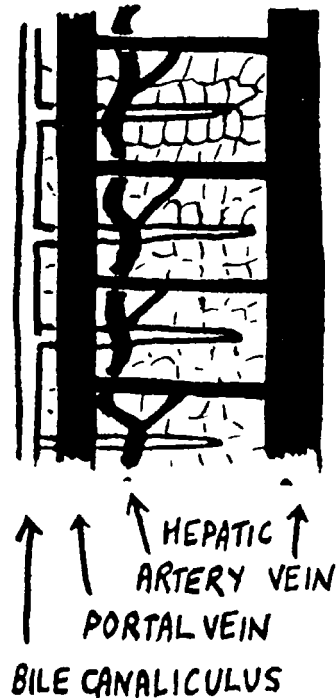
The third method can only be done at a well equipped cardiology centre.

Normal portal pressure is 10-16 cm. of saline, as measured by omental canulation, and a little higher on splenic puncture (12-20 cm. of saline). Temporary occlusion of the portal vein in a normal subject will cause the pressure to rise to 50 cm. saline, and pressures of 20-50 cm. saline are typical of portal hypertension.

Pathology

Causal conditions may be divided into three groups:—

- (a) Prehepatic venous occlusion, from within or without.
- (b) Intrahepatic sinusoidal obstruction, by inflammation or fibrosis—80% of cases.
- (c) Post-hepatic venous occlusion—very rare.



INTRAHEPATIC CIRCULATION

Fig. 2

Space does not permit me to give details, which can be discovered in any text-book on pathology. The pathological changes due to portal hypertension are as follows:

- (1) **Varices**—By far the most important of these are oesophageal varices, but, rarely, varices in the falciform ligament give rise to the interesting Cruveilhier-Baumgarten syndrome, and retroperitoneal varices may rupture giving a massive fatal haemoperitoneum. Haemorrhoids, for some unknown reason which apparently defies logic, are but a rare manifestation of portal obstruction. If a patient comes to you with haemorrhoids, start looking for a cause in the anorectal region, and not in the liver.
- (2) **Portal vein thrombosis**—Occurs in about 13% of cases, and may give rise to spreading mesenteric thrombosis.
- (3) **Splenomegaly**—This is thought to be due in part to the raised pressure, and in part to an actual hypertrophy. This latter theory is based on evidence obtained from transplantation of the spleens of rabbits under the skin of their abdominal walls, where a distinct hyperplasia was observed secondary to induced portal hypertension.

Clinical Features

These can easily be worked out from the pathology. The most important is *haemorrhage from the varices*, which may be sudden and torrential, preceded by a salty taste at the back of the mouth, or so slow that the only symptom is breathlessness due to the secondary anaemia. After the bleed the patient may pass into coma, either due to shock or due to neuropathy consequent upon the absorption of blood from the gut. Characteristically the bleeds are unpredictable, there being anything from days to years between them. The cause of bleeding has been attributed to:

- (a) Trauma of food particles,
- (b) Peptic ulceration (Learmonth),
- (c) Raised intra-abdominal pressure—which may increase the portal venous pressure by as much as 130 cm. of saline, for example in coughing.

Splenomegaly, in conjunction with a heavy haematemesis, and in the absence of a "peptic" history, should make one suspicious of portal hypertension. *Hypersplenism* is the condition of splenomegaly associated with anaemia, leucopenia and thrombocytopenia. This, with the hepatomegaly which sometimes occurs concomitantly, has been referred to as "Banti's syndrome," but this term should be abandoned now that the common factor of portal hypertension is recognised. Some of the *anaemia* is thought to be due to increased erythrophagocytosis of the cells which spend an unduly long time in the splenic pulp, but also blood is lost in the form of melaena, haematemesis and epistaxis. Thrombocytopenia is the barb upon the hook of oesophageal varices. No pathological process could have been more cunning than to provide a patient with a potential source of bleeding in the form of varices and then to deprive him of part of his clotting mechanism. If an experienced clinician, enwrapped in the worship of Bacchus, is unaware of this fact, what chance has the layman?

Ascites is not a feature of hypertension *per se*, but occurs if there is associated liver damage. It has been variously ascribed to a localised manifestation of a generalised fluid retention due to failure of the liver to inactivate sodium retaining corticoids, to increased vascular permeability

consequent upon the local hypertension, and to low plasma albumin, and is more evident when the obstruction is post-sinusoidal than in pre-sinusoidal block.

Signs of hepatic insufficiency may also be present. Thus there may be jaundice, with derangement of liver function tests, red palms, pigmentation of skin creases, spider naevi, xanthomata, and muscle wasting.

The collateral circulation may make itself evident in the form of a Caput Medusae in intrahepatic obstruction, or dilated veins in the scar of an abdominal operation. As mentioned above, haemorrhoids cannot be taken as a classical sign of portal hypertension.

Lastly, there may be symptoms of vague ill health—anorexia, mild indigestion, lassitude, and sometimes an ill-defined discomfort in the right hypochondrium.

Diagnosis and Investigations

The cardinal features of this disease are splenomegaly and haematemesis. There may be nothing else in the clinical examination to guide the physician, and often splenomegaly is the only evidence presented. But there remains a battery of investigations which should not fail to elucidate the true state of affairs within the abdomen.

- (1) **Liver Function Tests** may indicate that the liver is at fault, and help to decide the surgeon for or against a decompression operation (*v. infra*). It is important to realise that negative tests do not rule out liver pathology or portal hypertension.
- (2) **Barium Swallow** can be relied upon to visualise the varices as chains of rounded filling defects in at least 40% of cases.
- (3) **Oesophagoscopy** is suggested for doubtful cases, but I would hesitate to advise this for a patient with an acute bleed.
- (4) **Splenic venography** is perhaps the most decisive and useful test available, and is indispensable to the surgeon. Originally this was carried out via an omental vein at laparotomy, but recently the technique of percutaneous transsplenic venography has been developed, in which a few ccs. of opaque medium are injected into the splenic pulp, whence it is swept into the portal system which is therefore visualised. This is now a safe and effective procedure.

Only a few months ago a new approach to venography was made. This time the hemiazygos system was visualised by an intra-costal injection of opaque medium. This was claimed to be useful in difficult diagnostic problems, but its value remains to be confirmed.

- (5) **Liver Biopsy** may be done only when the information it yields is going to influence the management of the patient, and when the blood clotting mechanisms have been proved satisfactory.
- (6) **Peritoneoscopy** has been developed for use when malignant disease of the liver is suspected.

Treatment

Before treatment is begun the diagnosis of hypertension with normal liver function, or hypertension with damaged liver should be established. This done, treatment is aimed at

- (1) Stopping the bleeding if it is occurring.
- (2) Management of liver insufficiency if present.
- (3) Reducing the portal pressure by surgical means.

But it must be realised that no treatment, in our present state of enlightenment, will in any way alter the course of hepatic pathology, and we can provide only temporary relief. We can guide our patient safely through the rapids, but inevitably Niagara draws nearer.

Firstly, the patient with signs of portal hypertension: the non-operative methods of reducing portal hypertension consist in:—

- (a) A low salt diet (less than 5 grams per day).
- (b) Diuretics, either mersalyl or chlorothiazide.

Recent workers claim that quite dramatic results can come from treatment with chlorothiazide, but we have to face up to the chronicity of this disease, and I think it would be fair to say that diuretic drugs have their place in cases of acute hypertension due to active hepatitis, during the pre-operative phase of chronic cases, and in patients for whom surgery is for some reason contra-indicated.

What can he eat? With impaired liver function and in the absence of hepatic failure, he should be given a high protein diet with plenty of carbohydrate and added glucose. He must abstain completely from alcohol, and iron should be given to help him correct his anaemia.

More often portal hypertension presents itself as an acute emergency—as a haematemesis. The immediate measures to be taken are: rest in bed, transfusion and sedation. Care must be taken with morphia, which is detoxicated in the liver, and no more than 8 mg. should be given subcutaneously. Apart from this one drawback it is an admirable drug.

Having set up a blood drip, or plasma if there is no time to wait for blood, the next thing is to stop the blood loss. This is done by means of a Sengstaken-Blakemore tube, a three lumen tube with oesophageal and gastric balloons. The tube should not be left in situ for more than three days, since sloughing of the mucosa will then occur.

A large quantity of blood has been lost into the gastrointestinal tract, and this is liable to give rise to hepatic coma due to reabsorption of nitrogenous products from the gut. As much of this as possible is removed via the gastric tube and by enema, and 1 gram of Neomycin Sulphate should be given in an attempt to reduce nitrogenous metabolism of the gut flora.

Once resuscitated, the patient will have to undergo full investigation in order to decide future management—surgery or not.

We have now to consider the cold case—who has probably had one or two haematemeses, who is, at the moment, in fairly good general condition but whose future is, to say the least, doubtful. Into this category we may put our resuscitated patient mentioned above. We have come to the fork in the road—medical or surgical treatment?—and we do not know which way to turn. If we ask the sympathetic onlooker which way to go he will smile and say he's not very sure, and if we consult our map, it will show us that both roads come to an end not very far hence.

Let us first consider the lessons learnt from 15 years of surgery in the portal system. In the first year after operation there is, in fact, a marked reduction in the incidence of subsequent haemorrhage as compared with medical series. Thereafter there is little to choose, but perhaps a slight advantage exists in surgical treatment. The surgical approach to patients with advanced liver disease has met with uniformly bad results. Perhaps a look at the criteria which must be satisfied before operation is undertaken will help us to decide what to do:—

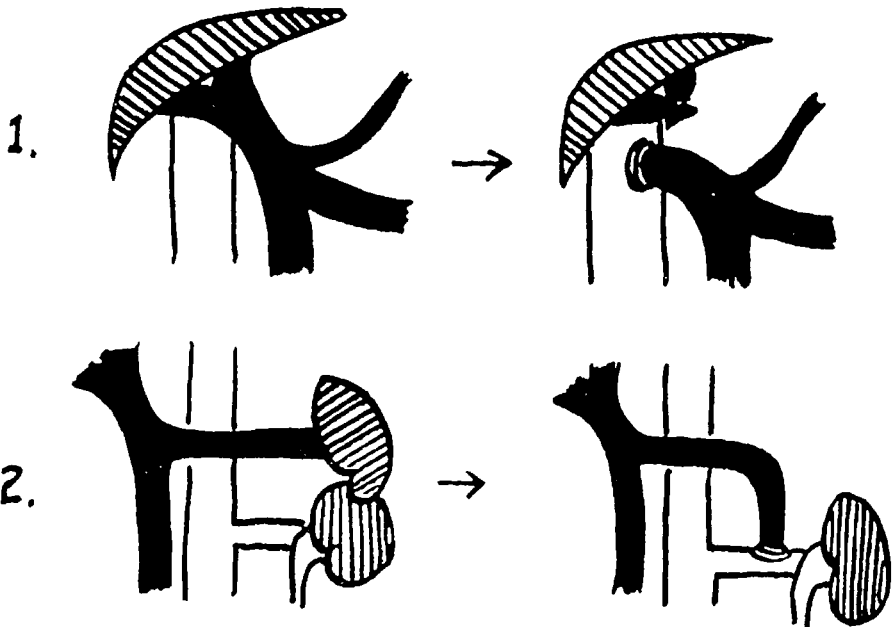
- (1) Age—patients over 60 years of age do not do well with surgery.
- (2) Recent jaundice—contra-indication.

- (3) Active liver disease—a contra-indication.
- (4) Liver function tests—must show:
 - Serum albumin: not less than 3 gm. %.
 - Flocculation tests: if positive, must be only weakly so.
 - Bromsulphalein: must be excreted to 70% within 30 minutes.
- (5) Ascites and Oedema—which fail to respond to medical treatment are strong contra-indications.

If our patient does not fit these rather stringent criteria, then medical treatment along the lines I have described should be instituted.

The basis of definite surgical treatment is the creation of a porto-systemic anastomosis, thus allowing decompression of the portal system. Blakemore, the pioneer in this field, enunciated in 1945 three principles which still hold good:

- (1) That shunt operations are designed to treat haemorrhage, and not ascites.
- (2) That shunts must be large, the only useful veins for the purpose being the portal and splenic veins.
- (3) That a shunt will function better the nearer it is to the obstruction.



1. PORTACAVAL ANASTOMOSIS

2. SPLENO RENAL ANASTOMOSIS

Fig. 3

The Portacaval Shunt

This is undoubtedly the most efficient anastomosis, but that brings us up against the big problem of shunts straight away—the more efficient the shunt the more likely is neuropathy to develop. However, in view of the less satisfying results obtained from other procedures, it seems reasonable to hold to Milnes Walker's dictum that, having decided a shunt is necessary, the most efficient anastomosis possible should be created. The mechanics

of the anastomosis are shown in figure 3. As a decompressing procedure this works admirably, but it seems to me to be basically wrong to effect a total diversion of the portal blood (as in end-to-side anastomosis) from an organ which has a precarious oxygen supply at the best of times. The alternative of side-to-side anastomosis does not solve the problem, since on the reduction of pressure the flow of blood upwards from the site of junction to the liver becomes either non-existent or even reversed, a state of affairs that is conducive to thrombosis. It is a remarkable fact that all attempts at manometry have been made with the patient in the horizontal position, and it would be interesting to measure what effect the erect posture has upon the pressure gradient across an anastomosis,

In cases where hypersplenism is present in sufficient degree to incapacitate the patient some workers advocate preliminary splenectomy, which is often followed by a reversion to normal of the blood dyscrasia. If this is done it is imperative to ensure that the portal vein is capable of being used later as a shunt, since the alternative splenorenal anastomosis can no longer be done. In these cases I believe the Edinburgh practise is to perform a splenorenal anastomosis in the first instance.

The Splenorenal Shunt

Originally Blakemore used to remove the left kidney, but obviously this is unnecessary (see figure 3). The indications for splenorenal anastomosis at the present time are:

1. The indications for portacaval shunting, with
2. an unsuitable portal vein, or
3. severe hypersplenism, and
4. a large splenic vein.

It is a more formidable procedure, and less efficient as a shunt, and for this reason it was at one time advocated as the operation of choice on the basis that it produced the required decompression with minimal neuropathic symptoms, whilst conserving the normal hepatic inflow. However, because of the difficulty of thrombosis, this is no longer the operation of choice without specific indications.

Operations on the Varices

There remain a number of operations directed at the varices themselves, and which are resorted to when no suitable vein for anastomosis exists, or when neuropathy is a feature of the patient's illness. There are many such operations, and I propose merely to list them with a few comments here and there:

1. Injection via the oesophagoscope. This merely destroys valuable porto-systemic connections, and raises the pressure in those that remain.
2. Gastric transection.
3. Oesophageal transection with splenectomy.
4. Ligature of the varices as an emergency procedure.
5. Limited Oesophago-gastrectomy of use when other operations have been or cannot be attempted.
6. Omentopexy—worthless.
7. Ligature of the hepatic and other (splenic) arteries has been advocated in Russia in preference to shunt operations for patients with cirrhosis, but after a few unsuccessful trials has commanded no great popularity in the West.

All these methods fail to prevent the recurrence of bleeding, later if

not sooner. Linton's idea that emergency ligation of the varices should give 3-4 weeks in which to improve the patient's condition prior to anastomosis seems sound, but even he himself did not suggest it as definitive treatment.

Portal Neuropathy: Theories

As I mentioned earlier, the great difficulty of portal decompression is the likelihood of producing neuropathy by shunting the unfinished work of absorptive metabolism into the systemic circulation where the rough rocks of protein breakdown are crashed upon the gravel path of cerebral metabolism. Or so it seems, for even yet we are not certain of the real cause of portal neuropathy. A rather inconstant relation with arterial ammonia concentration has been demonstrated, and patients being treated with Neomycin may suffer a rise in the blood ammonia level without clinical deterioration. It seems certain, however, that nitrogenous materials are causally related, since the two main precipitating factors are hæmorrhage into the gastro-intestinal tract, and a heavy protein meal, but what these materials are, and what is their relationship to intestinal, liver and cerebral metabolism, nobody is yet prepared to say. Keto acids and amines have been accused, but not as yet proved guilty. There still remains the alternative that portal encephalopathy may be due to a deficiency, rather than an excess, of some factor: 5-hydroxy tryptophane has been suggested as a possibility in this sense.

Results of Surgical Treatment

The operative mortality has been variously reported from 9-15%, being lowest in splenorenal anastomosis because that operation is often done in cases of extrahepatic obstruction without gross liver damage. The main causes of fatality, according to Blakemore, are:

1. Hepatic failure and neuropathy.
2. Operative hæmorrhage.
3. Mesenteric thrombosis.
4. Recurrent hæmorrhage.

A good demonstration of the superiority of portacaval anastomosis over the splenorenal type is given in Eckman's figures, in which 14 out of 32 patients with splenorenal anastomosis had recurrence of bleeding, while no recurrence at all was observed in 20 patients with a portacaval shunt, who were followed up for between one and seven years.

The functional result is on the whole good, and it has been demonstrated here in Edinburgh that liver function is only temporarily depressed after anastomosis, and that no more than after gastrectomy. However, I would question anyone who asserted that *no* liver damage occurred in man; permanent damage certainly ensues in dogs subjected to a similar insult.

Prognosis

In his classical series on the dietary treatment of cirrhosis, Patek concluded that 18% of all cirrhotics died of gastro-intestinal hæmorrhage, and that about 50% of patients who bled were dead within a year of their first bleed. Other writers give different results, some more and others less favourable, but even the most optimistic figures demonstrate the hopelessness of this condition 20 years ago, and though we have come a long way on the road to success, this is no time to rest on our laurels. It appears that in this condition, as in so many others, we must turn to the biochemist and the serologist to unlock for us doors that are as yet closed.

RES MEDICA

MAY 1960

The George Bernard Shaw Syndrome

Bernard Shaw really believed that a medical degree was a licence to kill. In a famous tirade written in 1906, he triumphantly proved that all doctors are humbugs and morally, if not always legally, criminals. Not only that, but "to make matters worse, doctors are hideously poor," and—just in case you happened not to appreciate what a terrible crime yours is—he added that "the greatest of our evils and the worst of our crimes is poverty, and our first duty, to which every other consideration should be sacrificed, is not to be poor." But Shaw must have felt that the great crime of poverty was not entirely the doctor's fault for he had yet more telling ammunition to fire. In accusing the profession of being unscientific and unkind, he touched two of the points upon which doctors over half a century later remain most sensitive. So much for G.B.S.

All this presented itself for reconsideration when we read again *The Doctor's Dilemma* early in October 1959. It was not fortunate reading for the time of year, and we have frequently regretted that a more benign drama had not come our way. Like spilt milk, however, it does not merit tears and we have had to adjust ourselves to passing our fifth academic winter at the University of Edinburgh labouring under rather eccentric standards. Is that doctor a pauper? Is he unscientific? Is he unkind? And the vital statistic that emerges is that the man who commands three direct negatives is a freak.

Now it is obvious to us, and, we imagine, to all readers, that the standards by which an enemy of the profession condemned medical men in 1906 are hardly those by which an undergraduate should be assessing his teachers, friends and colleagues in 1960. But where Shaw got three affirmatives in 100% of cases, our series has been more encouraging. The first question is no longer valid (his poverty, if it exists, is not nowadays the personal crime of the doctor). Most take a point from either the second or the third and there are even a few oddities who snatch a pair—kind doctors who are also scientists. Who have they turned out to be?

Sir Sydney Smith and Dr W. Ritchie Russell come to mind. *Mostly Murder* has now been devoured by the profession and the laity alike—and it is a book that must be devoured, for more leisurely reading cannot keep pace. Fact remains stranger than fiction and becomes stranger than ever. This is a classic biography and a key-chapter in medico-legal history. It is also something else, it is the record of a medical man who has been an original contributor to science, but whose work has been stimulated by a strict enthusiasm for human justice and impartiality. His is the story of a man who has spent his whole life helping people who he felt most needed his skilled help: the story of a kind doctor with a difference.

As eminent in his line as Sir Sydney is Dr Ritchie Russell, whose address on "Brain Mechanisms and Social Problems" is published in this issue of *Res Medica*. We were present to hear Dr Russell address the Society in December, and were delighted with his application of the exciting new discoveries of neurophysiology to the art of learning to live and become socially acceptable. Another rare case of humanity and science in the same

doctor. Dr Russell, himself a medical editor, has also taken a welcome and generous interest in *Res Medica* this year and his kind advice has helped us towards a better Journal.

We would like to forget for a paragraph that they are not quite doctors to include in this select list two unrelated and very different men—John and David Clark. Both are scientists in the best tradition of the new medical generation; both must be popular for patients are already reported to be swearing by one and with the other; both claim to be paupers—but we are suspicious. As Senior President, John has devoted much of his final year to the affairs of the Royal Medical Society, has personally attracted many new members, and has, not least, been a social hit. David was our ambitious and successful predecessor as Editor of *Res Medica*. He has also been secretary and President of the Society, and his liberal friendship and concern have been and are valued by us personally and by the Journal and the Society alike.

We can draw a favourable conclusion to our research—that the standards of Shaw have come, in 50 years, to apply more happily to the medical profession. There *are* doctors who are both scientific and kind. The revolution of 1948 has secured the medical man an income irrelevant to his labours, which makes him just as poor or rich as his colleague doing the same job. And this brings us round to another man who, like Shaw, has no medical degree, but whose name is safe in medical history. Aneurin Bevan, founder of the National Health Service, is now, we trust also a champion of the science and humanity in medical men. George Bernard Shaw, winner of the Nobel Prize for literature, *v.* Aneurin Bevan, P.C., M.P., might well have been quite a medical argument.

* * *

Poets and Cardiologists have long competed for the copyright of the heart, and William Wordsworth is quoted more than once by Dr R. W. D. Turner in his article on "Auscultation" in this issue. This is the first of a series of three articles by Dr Turner which will appear in consecutive numbers of *Res Medica*, the other two to be entitled "Triple Rhythm" and "Murmurs." This series should be particularly popular with both undergraduates and post-graduates alike and together they will provide a simple, yet comprehensive, account by a national authority on the vital art of using the stethoscope. From student to doctor is an overnight transition, but from guessing-tube to stethoscope is the work of years.

Addiction

There is no doubt that the risks of unlimited administration of the opiates are given sufficient emphasis in the instruction of the present-day medical student. There is current a picture of the drug addict, a man crazed and desperate, physically, mentally and morally degenerate, which is ever in the mind of the physician using these drugs. This, together with the doubt as to how prolonged a course is sufficient to precipitate addiction, may, in fact, combine to make a less experienced physician over-cautious, and fail to relieve pain where this is eminently and safely possible.

That a student should leave his school with a healthy respect for these most useful and most humane of all drugs is undoubtedly a very good thing. It is far better to start with timidity than with over-confidence. The strange thing, however, is that there are few addicts to opiates in this country, and of those who are, a small minority derived their initial stimulus from the medical profession.

There exists another group of addicts, in the true sense of the word addiction, who are much more common in this and other countries. A large majority of these people derived their supplies initially for a trivial illness from members of the medical profession. The barbiturate addict is a member of a large and ever-growing body of people.

Repeated estimates have deduced that about 10% of all prescriptions on E.C.10 contain a barbiturate as the main or only constituent. The production of barbiturates in this country in 1946 was estimated to be sufficient to provide one million people with a tablet a day for the year; within ten years the estimate had doubled, and no account was taken of barbiturates imported into the country from elsewhere. The incidence of suicide from overdosage has been steadily rising for the last thirteen years—ever since the inception of the National Health Service—and the most recent analysis suggests that 13% of all suicides, 75% of all drug suicides, and 80% of all fatalities from drug overdosage are caused by barbiturates. Finally, beyond the range of statistics, it is left for us to wonder how often barbiturates are administered with homicidal intent. The overall picture is not reassuring.

It has been suggested that the barbiturates have come to represent for the General Practitioner a cross between a placebo and a panacea. The psyche is now implicated in so many, and so diverse complaints, and is subject to so few therapeutic curtailments, that sedation is often the only remedy available—and is often successful, at least initially. Moreover, there are few diseases associated with sleep disturbance, where an uninterrupted night's rest does not produce beneficial results. Unfortunately it is often the patient with a psychosomatic disorder, or a sleep disturbance who has the underlying personality defect which predisposes to addiction.

A particularly pernicious form of this disorder is where there is a combination of drugs. Opiates and barbiturates are fortunately seldom used together by addicts in this country. Alcohol and barbiturates (the two share many clinical effects and may even affect the same biochemical processes) or barbiturates and amphetamines are more common combinations. The old joke about the socialite torn between taking a barbiturate and going to bed, or an amphetamine and going to the party, has now more sinister overtones.

As is so often the case, the diagnosis and even the prevention of these tragic medically induced illnesses rests more upon the awareness of the risks inherent in prolonged barbiturate administration than upon the recognition of any complex clinical syndrome. In particular the initial symptoms of intoxication may mimic those for which the drugs were first prescribed, encouraging further prescription, and the establishing of a vicious circle leading eventually to habituation and addiction.

Examining Exams.

During the past two hundred years medicine has developed from an art to a science. At the same time the different fields of study within the all-embracing subject, medicine, have expanded greatly in scope. Due to this gigantic increase in subject matter medical students are faced with a choice; either to study to the exclusion of all else or to attempt to cultivate outside interests at the same time as pursuing the curriculum. The average student will be unable to take the latter course and expect to do well in the professional examinations.

The duty of a medical school to the public is to ensure that its products are an asset to public safety and not a liability. A doctor who has wide cultural interests but a comparatively sketchy knowledge of medicine is a liability; he may have a good bedside manner but will only be able to help his patients die easily whereas a doctor with less charm and more knowledge may preserve the patient's life and, in all probability, give less satisfaction.

Examinations are the only possible way of ascertaining a student's grasp of the different branches of medicine. Examinations, considering that they are the only method of deciding whether the candidate is suitable to take on the responsibilities of a doctor, should not only test the student's factual knowledge at a particular time but should also determine whether he has a firm understanding of his subject.

The present system of examinations is open to criticism on both points mentioned above. The examination takes the form of a number of essay questions usually allowing a slight degree of choice. The essay form of answer is particularly poor in ascertaining the amount of knowledge the candidate has absorbed. Good style and the adroit use of a few facts can cover many important gaps. Another criticism of the present system is that the date of the examination is known beforehand. This allows the student to depend on last minute cramming. What is soonest learnt is soonest forgotten. It is unfortunate that the present state of the medical curriculum allows a student with a poor knowledge of a subject such as biochemistry to do well in a branch such as psychology or surgery.

Thus we would suggest that an examination paper should be of the short question-and-answer type. This would ensure that the student's knowledge was being tested and not his writing ability. (Useful though the latter may be, it is of little importance to a doctor as compared to the former.) These papers should be set at frequent intervals during the course testing the knowledge of the student up to that time. Our second suggestion is that students should not know the date of these examinations. This would avoid last-minute swotting and encourage continuous though perhaps less arduous study. In the long run this system would benefit the student with respect to his extra-curricular interests. He would be in a far better position to estimate his progress and the amount of time necessary to reach the desired standard, and hence the amount of time he could safely devote to other subjects.

Tradition

Any society which has been established for the best part of 200 years cannot help but evolve its own peculiar customs and traditions. In the minds of most people this tradition is pleasant and even worthwhile, yet in some there lurks an element of doubt which occasionally bursts in the form of caustic and unbridled criticism.

Vanburgh, the great 18th century architect and builder of Blenheim Palace, once said "Custom is the law of fools." Nowadays the cult of "all things contemporary" is much to the fore and tradition, particularly in the field of design, is seen in the unkindly company and light of Victorian conservatism. This lust for change and reaction against conformity has, however, spread beyond design, through art, into the realms of social conduct where it is not so refreshing and constructive.

Before altering any old tradition much thought and debate is necessary. All too easily something old yet good and functional can be thrown out and sacrificed to this modern Goddess of Change, only to be regretted after the irreversible deed is completed.

AUSCULTATION OF THE HEART

I

BY R. W. D. TURNER

O.B.E., M.A.(Cantab.), M.D., F.R.C.P.Ed., F.R.C.P.Lond.

“And the babe leaps up on his mother’s arm
I hear, I hear, with joy I hear.”

Wordsworth.

All students find initial difficulty with auscultation and to some, variations in heart sounds and murmurs remain a mystery. However, given normal hearing, a good stethoscope, an appreciation of underlying mechanisms and reasonable opportunity to practise, everyone would become sufficiently competent. The essential requirements are a methodical approach and attention to detail and then, if what is heard is accurately recorded, the correct diagnosis should follow in most cases.

It is important to be able to recognise variations in the intensity and splitting of the heart sounds, the physiological and pathological forms of triple rhythm and the murmurs associated with valvular stenosis or incompetence and with congenital cardiac and vascular defects.

Recognition of auscultatory phenomena is important not only for accurate diagnosis but to avoid errors of interpretation and, in particular, the frequent error of suspecting or actually diagnosing heart disease when none is present and thereby engendering anxiety and imposing unwarranted restrictions.

Undergraduates, of course, find difficulty from lack of experience. However, difficulty is often largely due to lack of a good technique and to lack of appreciation that there is a rational and usually simple explanation for all that can be heard.

Postgraduate students are often more familiar with what they have been told or read than with bedside observation and tend to find physical signs which they consider ought to be present rather than to record what can actually be heard.

More senior physicians often find difficulty because they were trained before the days of modern precision which is due to the more accurate analysis made possible by phonocardiographic studies and the stimulus to accuracy provided by cardiac surgery and the special techniques employed to establish pre-operative diagnosis.

Sometimes undue attention is given by specialists to what might be termed the minutiae of auscultation which is more often an academic study than of practical value, because so often at the bedside there is a difference of opinion over details even between practised observers. On such occasions phonocardiography is as indispensable to auscultation as electrocardiography is to the interpretation of arrhythmias, but most often it is used as a research technique. Theoretical concepts are not always fulfilled in practise.

Stethoscope

It is surprising to find that some students still possess a stethoscope with only a bell chest piece. Anyone having doubts as to the value of a diaphragm will soon have them removed by comparing the relative intensity of a high pitched murmur with both types of chest piece. The best example is the

familiar early diastolic murmur of aortic incompetence. Such a murmur is always better heard with a diaphragm and if faint may not be audible at all with a bell. Similarly the low pitched rumbling mid-diastolic apical murmur which is characteristic of mitral stenosis is more readily heard with a bell and may be missed altogether with a diaphragm.

Probably the best stethoscope is Leatham's modification of the Sprague-Bowles variety. By means of a small lever one can switch conveniently from bell to diaphragm without detaching the end piece. The bell is designed to accentuate lower frequencies by filtering out the higher frequencies and the diaphragm responds best to higher frequencies. The length of tubing is also important, the shorter the better. A length of 10-12 inches is suitable, with an internal diameter of $\frac{1}{8}$ th inch. Ear pieces should fit snugly so that the best size will vary between individuals.

One further point as regards the use of the stethoscope may be mentioned and that is that variation in the pressure with which the end piece is applied to the chest wall makes a considerable difference to the ease with which different sounds and murmurs may be heard.

There is no mystery about these findings which are based on simple physical principles.

The practise of medicine is sufficiently complex without adding difficulties by inadequate equipment and the small extra financial outlay will pay good dividends over the years.

Technique

Practise tends to make perfect but everyone will agree that all the practise in the world will not necessarily make a good musician or golfer or physician. Nevertheless skill in auscultation does come with practise and every beginner will be surprised at how much can be heard once something has been pointed out and once the lesson has been learned of listening methodically to one thing at a time.

It is best to begin by concentrating on heart sounds in each of the four conventional "areas." The first heart sound is best heard at the apex (mitral area) and at the lower left sternal border (tricuspid area). The second heart sound is best heard at the base to the right of the upper sternum (aortic area) and to the left of the upper sternum (pulmonary area).

Then, forgetting about heart sounds, attention should be paid to murmurs first in systole, that is between the first and second sounds. It is a good plan, having detected the presence of a murmur and its position of maximum intensity, gradually to "edge" the stethoscope out in each direction to note its "propagation" or "conduction." In some circumstances this procedure greatly facilitates diagnosis. For example, if a systolic murmur is loudest at the mid or lower left sternal border and can be traced to the aortic area it is almost certainly due to aortic stenosis. If an apical systolic murmur is conducted to the axilla or beyond to the left lung base it almost certainly derives from mitral incompetence.

In general, of course, a murmur is "conducted" in proportion to its intensity.

The Discipline of Auscultation

"And sanctifying by such discipline
Both pain and fear—until we recognise
A grandeur in the beatings of the heart."

Wordsworth.

Are both heart sounds present, and if so, is each normal? If not, is

the first sound louder or weaker than normal (or absent) or split? Is the second sound louder or weaker (or absent) or split? Are there more than two heart sounds? If so, is the extra sound in systole or in diastole?; and nearer the first or the second sound?; and what is its quality? Is it preceded or followed by a murmur?

If a murmur is heard there should follow a similar mental catechism. Over what area is it audible and where is it loudest? In which direction is it next loudest (or "conducted") and how far from the position of maximal intensity can it be heard? What are its time relationships to the heart sounds? Is it systolic or diastolic? If systolic does it occur in early, mid or late systole or is it pan-systolic? If diastolic is it early, i.e. immediately following the second heart sound, or mid, i.e. after an appreciable gap from the second sound, or late, i.e. pre-systolic? As will become clear when dealing with individual defects and diseases each of these features has a particular significance in diagnosis.

Some attempts at grading the intensity and describing the qualities of a murmur should always be made. It does not matter how many grades are used by different observers so long as the standard is stated. This can easily be expressed as a fraction. If, for example, a systolic murmur is recorded as Grade 3/5 intensity this signifies that the maximum number of grades recognised by the observer is 5—the faintest being Grade 1 and the loudest likely to be heard is Grade 5 so that the murmur in question is a moderately but not very loud one. The three grades faint, moderately loud and very loud sometimes used are not really sufficient if changes from time to time are to be recorded.

As regards quality it would be helpful if agreement could be reached over adjectives, and preferably their number should be restricted.

It is suggested that it would be sufficient to use the term blowing, harsh or rumbling and high or low pitched with a few additions for unusual murmurs such as whistling, musical or raucous.

Phonocardiography

Phonocardiography is the graphic registration of heart sounds and murmurs. A piezo-electric microphone is placed on the chest wall and the vibrations produced by the heart are picked up, transmitted, filtered, amplified and recorded.

The crystal has the property of converting sounds or pressure waves into electric currents and responds fairly uniformly over the range of frequencies required in phonocardiography.

Phonocardiography has brought precision to auscultation and having laid the basis for the correct appreciation of auscultatory findings is now rarely necessary in practise. It is principally useful in cases of dispute for teaching and research and in special cases where permanent or serial records are required.

Phonocardiography is no substitute for auscultation.

Genesis of Heart Sounds and Murmurs

It is generally assumed that heart sounds are due to vibrations set up by abrupt changes in the velocity of the blood stream. Valve closure suddenly arrests or reverses the movement of blood and plays a major role in the genesis of the normal heart sounds.

Murmurs are thought largely to result from turbulence in a rapidly flowing stream of blood.

From the clinical aspect heart sounds appear very short, but from the

phonocardiographic point of view there is no clear dividing line between sounds and murmurs which are mainly distinguished by duration.

Heart Sounds

The first heart sound is mainly produced by closure of the mitral and tricuspid valves when the ventricular pressures rise above that of the atria.

The second heart sound is due to closure of the aortic and pulmonary valves when ventricular pressures fall below that in the great vessels.

Normally mitral and aortic valve closure are louder than tricuspid and pulmonary valve closure and this in part may be related to the greater pressures on the left side of the heart.

Both heart sounds may be difficult to hear on account of:

1. Thickness of the chest wall.
2. Increased antero-posterior diameter.
3. Emphysema.
4. Pericardial effusion.
5. Decreased force of cardiac contraction.

Qualities of the Heart Sound

The following properties should be noted.

1. Increased intensity.
2. Decreased intensity or absence.
3. Varying intensity.

Intensity of the First Heart Sound

The intensity of the first heart sound is mainly dependent on the position of the valve leaflets at the onset of ventricular systole, and on the force of ventricular contraction. If the valve is wide open and the cusps are far apart and have a relatively long way to go in order to shut, the closing sound will be relatively loud but if they are close together it will be relatively faint. The cusps will tend to be far apart if ventricular filling is prolonged, e.g., from valvular stenosis or increased blood flow or if the A-V conduction time is short.

The first heart sound tends to be **loud** with tachycardia from any cause such as exercise, emotion, fever or anæmia, and in other hyperdynamic circulatory states such as thyrotoxicosis.

In mitral stenosis the first heart sound is characteristically loud and "slapping." This in part is due to prolongation of atrial systole with the result that the valve leaflets are deep in the ventricle at the onset of ventricular systole, partly to the shortened chordae tendinae holding the leaflets back and in part to the fact that the cusps are thickened as a result of rheumatic endocarditis.

By contrast a relatively quiet first sound (when not due to such factors as a thick chest wall, emphysema or pericardial effusion) may be due to prolongation of diastole so that the cusps have had time, so to speak, to float together, and consequently make little sound by their apposition. This will occur with bradycardia. In mitral incompetence either the leaflets will not come together at all from structural defect or from widening of the valve ring or they will do so imperfectly and as a result the first sound will be absent or weak.

Similarly, **variation in intensity** of the first sound will be present if there is dissociation between atrial and ventricular contraction such as may result from complete heart block, atrial flutter or ventricular tachycardia when the atria and ventricles beat at different rates.

It will be appreciated that the intensity of the first heart sound bears an inverse ratio to the atrio-ventricular conduction time as reflected in the P-R interval of the electrocardiogram, that is, the shorter P-R interval the louder the sound.

Intensity of the Second Heart Sound

Increased intensity of the second sound at the base of the heart may be due to systemic or pulmonary hypertension. Actually the relationship is not a direct one and there are usually other factors operative which influence the intensity. Thus the aortic second sound is by no means always loud even in severe systemic hypertension, loudness being much more often associated with atheroma and in some cases of severe pulmonary hypertension from mitral stenosis the pulmonary second sound may not be loud, possibly from decreased blood flow.

Since the second heart sound is due to closure of the semi-lunar valves, **decreased intensity** or absence of the sound will result from deficient closure. Thus the aortic second sound may be weak or absent from aortic stenosis or incompetence and in such cases the second sound in the pulmonary area (which is often finely split since closure of both valves can be heard here) will be single. If the pulmonary second sound is loud (from pulmonary hypertension) in such cases of aortic valvular disease, this will be heard to the right of the sternum. The pulmonary second sound may be weak or absent from pulmonary stenosis. Since pulmonary incompetence is almost always due to severe pulmonary hypertension the second sound in such cases is loud.

Physiological Third and Fourth Heart Sounds

A third heart sound early in diastole, that is shortly after the second heart sound, can often be heard in young people.

A fourth heart sound late in diastole (pre-systole), that is just before the first heart sound, can usually be recorded by phonocardiography but is rarely audible. These two physiological sounds are described later in the section on triple rhythm.

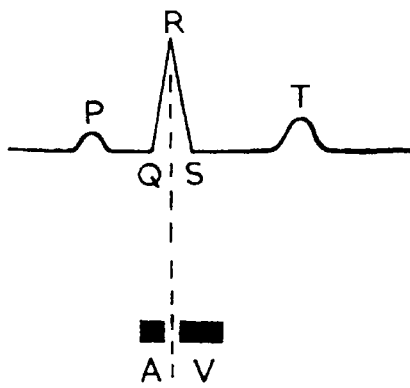
Splitting of the First Heart Sound

The first heart sound is not a pure harmonic vibration but is composed of a number of unrelated frequencies. Normally four components can be recorded but only two are heard. The first component may be due to atrial vibrations, as usually described, or be of muscular origin, as more recently suggested. The second and third components may be heard separately or as one sound and coincide with isometric contraction of the left and right ventricles respectively. It is now generally agreed that these sounds are due to closure of the mitral and tricuspid valves. The last or fourth component is probably due to systolic ejection of blood and may be vascular or valvular in origin.

Physiological splitting of the first heart sound is due to slight asynchrony in ventricular contraction and therefore in mitral and tricuspid valve closure, and is a normal phenomenon.

This can often be appreciated in healthy subjects by listening at the lower end of the sternum, which is the position where the stethoscope is nearest to the relatively quiet tricuspid component, and paying particular attention to expiration when there is relatively little lung tissue between the heart and chest wall.

The importance of a split first sound lies in its recognition and in differentiation from other conditions.



1st. HEART SOUND

A = ATRIAL COMPONENT
 V = VENTRICULAR "

Fig. 1

DIFFERENTIAL DIAGNOSIS OF SPLIT FIRST SOUND

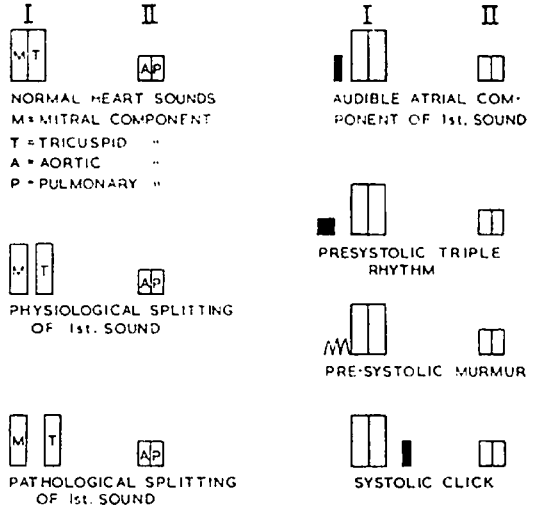


Fig. 2

Pathological splitting occurs in complete right bundle branch block when impaired conduction results in delay in tricuspid valve closure and hence in wide splitting of the heart sounds.

DIFFERENTIAL DIAGNOSIS OF SPLIT FIRST SOUND

Atrial Component of First Heart Sound

The atrial component of the first heart sound cannot usually be differentiated by ear, but in cases of partial heart block in which prolongation of the P-R interval reflects delay in A-V conduction this component may be heard and splitting of the first sound may be simulated.

Pre-systolic Triple Rhythm

Splitting of the first heart sound must also be distinguished from pre-systolic triple rhythm as discussed below. In splitting the two components are very close together and of somewhat similar quality, and in triple rhythm, the extra sound precedes the first heart sound by an appreciable distance and is of a different, lower pitched quality.

Pre-systolic Murmur

In mitral stenosis atrial systole results in a pre-systolic murmur at the apex. This murmur becomes louder when blood flow is increased by exercise or tachycardia from any cause. Most often such a murmur is associated with a loud first sound ("closing snap"), an "opening snap" and a mid-diastolic murmur, but in patients with mild stenosis only a slight pre-systolic murmur may be present, and in such cases there may be difficulty in differentiation from splitting of the first heart sound.

Systolic "Click"

Apparent splitting of the first heart sound may be due to the addition of an added sound or "click," synchronous with ventricular systole and due to vibrations in a dilated ascending aorta or main pulmonary artery.

In such cases the added sound is usually heard at the base of the heart in the aortic or pulmonary areas and occurs immediately after the second heart sound.

Splitting of the Second Heart Sound

PHYSIOLOGICAL SPLITTING

Physiological splitting of the second heart sound is due to slight asynchronous closure of the aortic and pulmonary valves.

During inspiration the normally negative intra-thoracic pressure becomes still more negative with resultant increase in the venous return to the right side of the heart. With deep inspiration this is exaggerated with resultant prolongation of right ventricular systole and delay in pulmonary valve closure. Consequently the second heart sound in the pulmonary area becomes more widely split and this can often be recognised in healthy people.

It can be shown by phonocardiography that the single second sound which can normally be heard in the aortic and mitral areas and also the first component of the normally split second sound in the pulmonary area is due to aortic valve closure. The second component in the pulmonary area is due to pulmonary valve closure.

PATHOLOGICAL SPLITTING

Abnormal splitting of the second heart sound is most often due to delay in pulmonary valve closure but rarely may also result from premature closure of the aortic valve.

Delay in pulmonary valve closure may result from delayed activation of the right ventricle or to prolongation of right ventricular systole. Activation of the right ventricle is delayed in right bundle branch block.

Prolongation of right ventricular systole may result from a relative increase in right stroke volume compared with the left such as occurs from a left to right intra-cardiac shunt through an atrial septal defect or from obstruction to outflow such as occurs with pulmonary stenosis. In such cases splitting cannot be further increased by deep inspiration and is usually described as being "fixed."

Early aortic valve closure may result from the decreased resistance to left ventricle outflow which occurs in incompetence of the mitral valve.

Splitting of the second heart sound must be differentiated from triple rhythm and from the opening snap of the mitral valve. In the latter instance there will also be present a mid-diastolic murmur. A mid-diastolic murmur may also occur without a preceding snap and if short may also cause difficulty in diagnosis.

(TO BE CONTINUED)

DIFFERENTIAL DIAGNOSIS OF SPLIT SECOND SOUND

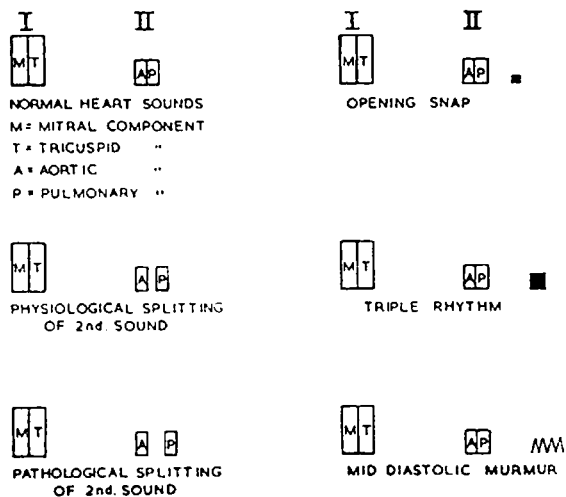


Fig. 3

Congenital Maldevelopments as a Cause of Hydrocephalus

BY DAVID DOYLE

Based on a Dissertation read before the Royal Medical Society on Friday, 13th October 1959.

(i) Incidence and Aetiology

The incidence of congenital malformation is difficult to gauge accurately. In Philadelphia, in the late 1930's, 2.9% of 7,478 cases of still-birth had malformations recorded on the death certificates. About the same time, a rate of 20.2% was derived from autopsy reports on 435 still-births in Edinburgh. The percentage of children who died in the neonatal period with abnormalities varied between 10.5% in Edinburgh, 2.5% in Glasgow and 13% in Belfast. There has been no increase in the incidence of congenital defect recently.

Hydrocephalus comes second to anencephaly as a cause of death from congenital abnormality.

The rarity of malformations causing hydrocephalus makes elucidation of aetiology difficult, but significant correlation has been found in some instances.

Much less clearly than with mongolism, the increased proportion of hydrocephalics born to mothers over 35 years of age has been noted. Between 1940-47 the incidence among children born to mothers in the 40-49 age groups was three times greater than among those of mothers under 30. Another series in 1947 showed that from mothers over 40 years the incidence was twice that from the under 30 group. It is not possible to dissociate birth rank from maternal age, because an increase only becomes apparent after the fifth or sixth pregnancy.

Congenital hydrocephalus shows no obvious distribution towards either sex, although one series showed a male:female ratio of 1.27:1. Hydramnios, and less often oligohydramnios, has sometimes been shown to be associated with hydrocephalic infants.

Lack of Vit. A increases the proportion of hydrocephalic young born to rabbits and, in rats, deficiency of Folic acid and Vit. B12 can be made to produce almost pure families with deformed aqueducts and hydrocephalus.

The high mortality rate from hydrocephalus does not lend itself to studies of hereditary trends, but some observations have been made. Mendelian recessive traits led to narrowing of the aqueduct in one family and retarded cartilage growth at the base of the skull in another. Obstruction of the Foramen of Monro is said to be hereditary.

More than one-third of congenitally hydrocephalic children present some other congenital malformation.

(ii) Pathology

Most of the errors of development occur at points in the cerebro-spinal

fluid channels where there is a constriction. They may represent failures of opening, delays in opening, or reclosing of a space.

Aqueduct of Sylvius—	Stenosis	(fairly common)
	Complex Forking	(common)
	Gliososis	(rare)
	Septae	(very rare)
Foramina of Magendie and Luschka—	Blockage	(common)
	Failure to open	(rare)
Dandy-Walker Syndrome—		(rare)
Arnold-Chiari Syndrome—		(very common)
Lissencephaly		(very rare)
Deformities of Skull—	Platybasia	(rare)
	Achondroplasia	(rare)
	Defects of Sutures	(rare)

Aqueduct of Sylvius

Stenosis is the least common aqueduct disorder causing hydrocephalus. Enormous variations in the diameter of the tube are encountered, and the foetal aqueduct is wider than the adult's. There are usually two constrictions in the aqueduct, one—0.4-0.8 sq. mm.—at the level of the superior colliculus, and another—0.5-1.0 sq. mm.—at the level of the intercollicular sulcus. With the merest pin-point of an aqueduct, people may live without trouble, others develop attacks of headache, vertigo, nausea and vomiting, while others may become frankly hydrocephalic.

Forking may be simple, in which case it is harmless and common, or complex, a common or certain cause of hydrocephalus. Many normal individuals have outpouchings from the dorsal, lateral or more commonly ventral walls of the aqueduct. These "simple forks" are blind tubes, not interfering with the patency of the main tube. In complex forking, on the other hand, both tubes divide repeatedly, establishing ineffective or no communication with the rest of the duct. The flow of C.S.F. from the third ventricle is stopped.

The branches of the aqueduct are separated by normal neural tissue. The corpora quadrigemina and third nerve nuclei are often fused. These facts have been taken to illustrate an exaggerated closure of the neural tube in this region.

Gliososis of the Aqueduct is uncommon. It often looks like a neoplasm and, since normal people often have rests of ependymal cells in the surrounding neural tissue, it could be a neoplasm of these cells. Basing their argument on the widespread ependymal disorder which often occurs with gliosis, some hold this to be part of the aftermath of a foetal ependymitis.

Gliososis is common in cerebral diplegia, with and without hydrocephalus.

Septae of neuroglia across the aqueduct have been reported.

Foramina of Magendie and Luschka

The Foramina of Magendie and Luschka may be imperforate at birth, or may have been closed again by toxoplasmosis or congenital syphilis. Even if the foramina do not break through, severe degrees of hydrocephalus are not the rule; sufficient fluid is able to cross the membrane under ordinary conditions to maintain a balance compatible with adult life in many instances. These subjects, if not hydrocephalic, show a tendency to sudden pressure elevation caused by such diverse factors as physical exertion, alcoholic bouts, fatigue and menstruation. They are, of course, poorly placed should they develop a serous meningitis.

When the foramina are absent, defects of the medulla and cerebellum are common.

The Dandy-Walker syndrome is one in which there is hydrocephalus with deficiencies of the cerebellar vermis. In the embryo, when the cerebellar anlagen migrate across the roof of the fourth ventricle, they fuse anteriorly first. Stretching of the roof membrane might delay fusion of the posterior parts. If bulging, caused by raised C.S.F. pressure, is the cause of the cerebellar defect, the C.S.F. production must begin inordinately early, because the fusion of the anlagen is complete before the foramina are due to open. Their opening is related in time to the beginning of function of the choroid plexuses at the fifth month of intra-uterine life. This syndrome is easy to recognise. The occiput is long; the lateral sinuses and tentorium are elevated; ventriculography is distinctive. Fortunately, it is especially amenable to treatment.

The Arnold-Chiari syndrome of hydrocephalus with cerebellar displacement and meningocele is a common cause of hydrocephalus. About 20% of hydrocephalic infants have meningoceles and, if one appears at a breech presentation, a hydrocephalic child must be expected.

Features of this syndrome are fusion of the cerebellar tonsils and their protrusion downwards through the foramen magnum over a long, lower brain stem to the upper cervical cord. The upper cervical roots are angled upwards, and the medulla is inclined backwards on the cord. There is invariably a major degree of spina bifida, and two-thirds of all cases have microgyria.

The cerebellar tissue involved in the deformity is hypoplastic, and the small cerebellum lies in a small posterior fossa—craniolacunia. The cerebellar abnormality does not seem to contribute to the hydrocephalus. The smallness of the posterior fossa seems to cause enlargement of the posterior horns of the lateral ventricles.

The leptomeningeal vessels—especially, but not entirely, the veins—overlying the cerebellar deformity are increased in number and size. Half of all cases have abnormal vessels in the mid-brain.

The causes of hydrocephalus in this syndrome are complex forking of the aqueduct in some, and probably hindbrain compression because of the smallness of the posterior fossa. Some may have impaction of the foramen magnum because of the cerebellar and vascular structure around the opening. A contributing factor may be that the exit foramina of the fourth ventricle are below the foramen magnum.

Why these abnormalities should occur in such constant partnership is not known. Lichtenstein's theory of traction from below is untenable because, even without a fixed meningocele, upward angling of the cervical roots may occur. This angling occurs in the Klippel-Feil syndrome of congenital short neck. One theory is that there has been pressure on the foetal head during intra-uterine life, squeezing the hind-brain through the foramen magnum. There is, however, no relation between the amount of basilar impression and the degree of cerebellar displacement.

There are seldom diagnostic clinical features of this condition. Cerebellar signs, such as mirror movements of the arms, unsteadiness, clumsiness and nystagmus are common, but not constant. Intermittent pressure increases are common in children and adults, bringing severe headaches—often precipitated or aggravated by coughing or sneezing—tinnitus, nausea and neck stiffness.

That the meningocele may maintain the balance between absorption and production of C.S.F. is debatable. Some series show that upwards

of 15% of those who have had them removed develop increased pressure. The sac may participate in absorption, but it may not be assumed that the removal of the sac alone causes pressure elevation.

Lissencephaly, or agenesis of the subarachnoid space, which normally opens after ten weeks of intra-uterine life, is added for completeness.

Another rare anomalous cause consists in large, detached masses of tissue lying free in the meninges. This is usually associated with neoplasia elsewhere.-

Malformations of the skull predisposing to hydrocephalus are rare.

In **Platybasia**, the angle between the basi-sphenoid and the basi-occiput is increased beyond the normal 130-140 degrees. The posterior fossa is foreshortened, the margins of the foramen magnum become inverted, and the odontoid process, appearing in the posterior fossa, impinges on the hind-brain. This occurs as a congenital defect, or may appear as a result of modelling of soft bone, as in osteitis deformans.

Achondroplasia, by altering the relations at the base of the skull, causes hydrocephalus.

Craniostenosis and **Oxycephaly**, conditions of abnormal fusion of sutures, reduce the capacity of the skull, and occasionally show elevated C.S.F. pressure.

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THE BIOLOGICAL BASIS OF INDIVIDUALITY

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Based on an Address delivered to the Royal
Medical Society on 23rd January 1959.

Philosophers have had much to say on the question of personal identity, though I must confess that I have not found any of it very helpful. Most of you, I suspect, would find yourselves in agreement with John Locke—whose robust common sense has I think a special appeal to medical men, perhaps because he was one himself—that we each have an intuitive knowledge of our own existence. Some of you, on the other hand, as good sons of Edinburgh, may prefer the sophism of David Hume, and affirm that man is nothing but a bundle of perceptions—though Hume himself later in life appeared to have doubts about this. Perhaps, though I hope not, a few of you may believe that Society or The State is the smallest unit worth bothering about, and that what we call an individual is merely an abstraction.

I am going to start with the common-sense assertion that all the higher animal species including man are made up of individuals, and that each individual is unique. Whether this holds good for lowly organisms such as bacteria I don't know, but for our present purpose it does not matter.

I am going to take it for granted also that the characteristics which distinguish different individuals are partly inherited, and partly the result of differences in environment.

You all know that the various tissues of the body are composed of cells and intercellular substance, and the question I want to discuss may be stated thus: To what extent are animal cells characteristic of the individual from whom they are derived? To put the matter another way: Mr Smith and Mrs Jones are different people, but is there something about an epidermal cell, a fibroblast or a chondrocyte from Mr Smith which distinguishes it from a cell of the same histological type from Mrs Jones? If so what form do these self-markers, as we may call them, take, and how can they be demonstrated?

There are two main approaches to this problem, which I shall call the **genetic approach** and the **immunological approach**, and these are becoming integrated in the newly emerging scientific discipline known as **immunogenetics**.

The basic concept of classical genetics, which dates from the time of Mendel, is the genetic factor or gene, which is a unit of inheritance often occurring in two or more forms each with a characteristic developmental effect. During the second decade of this century it was established that genes are carried in chromosomes and are arranged linearly, and following this a good deal of progress was made in the direction of correlating genetic and cytological observations.

The chemical composition of chromosomes was investigated and they were shown to be made up of desoxyribonucleic acid (DNA for short) and

protein, combined in a way that is still not completely understood. For many years it was believed that genetic specificity was determined solely by the structure and configuration of the proteins, but the demonstration in 1944 that transformation in type specificity of pneumococci could be brought about by highly purified preparations of DNA suggested that this substance might be the carrier of genetic information. A considerable weight of evidence in support of this hypothesis has now been accumulated, though in some plant viruses ribonucleic acid (RNA) appears to be the primary genetic material.

The DNA protein, according to one view, assumes the configuration of a double helix of two complementary polynucleotide chains which are capable of replication, and in which the genetic information is coded in the form of specific sequences of purine and pyrimidine bases. Gene function depends on the translation of DNA specificity into protein specificity, probably via an RNA template mechanism.

As you know changes occur in genetic coding as a result of a variety of processes—gene mutation, crossing over, and others of a more esoteric kind, and the question of controlling such changes constitutes a challenge for biologists comparable to those of nuclear physics for its devotees.

One method which has been used extensively is exposure to ionizing radiation, but it is a crude sort of procedure—just as radiotherapy and, for that matter, surgery are crude procedures, which in time will I think be largely replaced by more elegant methods of treatment.

Another approach arises out of the observation that genetic transformation in bacteria can be brought about by exposure to free DNA, or by the action of bacteriophage particles which carry genetic material from one bacterial cell to another in a manner which to the non-bacteriologist (and I might add non-apiarist) suggests the thought of bees carrying pollen from one flower to another. Can the same sort of thing be done with the germ cells of higher animals? You will remember that in 1957 Benoit and his colleagues in Paris said that it could in ducks. Most geneticists however have been publicly sceptical about this—one at least published some stern criticism in *The Scotsman*—but if you wander round the world you will find that a lot of experiments of the same sort are being conducted, and one has the feeling that some geneticists at least protest too much.

The standard genetic test for detecting changes in genetic coding in the germ cells of an individual is to study the characteristics of offspring one of whose parents is the individual in question. The choice of the other parent, and of the characters to be studied, depends on many factors which we need not consider here; the point I want to make is that the test is of decidedly limited application.

A more direct approach would be to try to demonstrate differences between the cells of different individuals. In theory this might be done chemically or cytologically, but in practice, as far as differences between individuals which are members of the same species are concerned, these methods do not take us very far. The chemical attack on the problem has begun with the recognition that there are several different human haemoglobin molecules, but the chances of distinguishing at present by this test between two people picked at random are extremely small. Similarly, cytological observations, though they enable us in some species to determine whether an epidermal cell or a polymorphonuclear leucocyte is from a male or female individual, and occasionally to recognize cells from members of an inbred strain by means of a characteristic chromosomal marker, are quite inadequate for our purpose of distinguishing routinely between randomly

chosen individuals. There remains the immunological approach, and I want to consider this in a little detail.

The basic method of investigation is transplantation, and this simple procedure has yielded results of quite remarkable importance. Let us look at the basic facts. If you take a piece of tissue and transplant it autologously, i.e. from one part of the body to another place in the same individual then as a general rule, if its nutritional needs are met, it will survive permanently in a new environment. A familiar example is that afforded by the skin grafts which are used in treating burns and for many other purposes in reconstructive surgery. If, on the other hand, the tissue is transplanted homologously, i.e. to another member of the same species, it typically survives for a time ranging from a few days to a few weeks, but sooner or later becomes invaded by cells of the recipient and is destroyed.

There are exceptions to this; for example transplants exchanged between identical twins behave like autologous transplants, and homologous transplants of cornea may survive indefinitely, probably on account of their avascularity, but the rule holds good in a very wide range of cases.

It was shown by Gibson and Medawar, and has since been confirmed by hundreds of investigators, that a second transplant from a given donor to the same recipient is destroyed more rapidly than the first. This suggests that the destruction of homologous transplants is an immunological phenomenon, and confirmation has been provided by the discovery of Mitchison that the state of increased resistance to transplants from a given donor can be transferred "adoptively" to a third member of the same species.

A good deal is now known about the antigens responsible for immunity to homologous transplants. It was thought first that they were DNA protein, like the units of genetic inheritance, but it now appears that they are complex polysaccharides which are normally carried on DNA protein molecules. They are determined genetically by a particular class of genes known as histocompatibility genes. Linkage has now been demonstrated in mice between histocompatibility genes and genes responsible for a variety of somatic characteristics, and this discovery forms the starting point for the new and rapidly developing science of immunogenetics.

The search for antibodies in the serum of recipients of homologous transplants has proved less rewarding. There is abundant evidence that the cells of the recipient play an essential role in the destruction of such transplants, and even when humoral antibodies can be demonstrated it often remains doubtful whether they play any part in the destructive process.

It is natural to ask why, if what has been said is correct, the mammalian foetus, part of whose genetic inheritance is derived from the father, is not treated by the mother as a homologous transplant and destroyed. It has been shown that there are several factors which help to prevent this catastrophe, the most important being the existence of a barrier in the placenta which normally prevents maternal cells from entering the foetal circulation and vice versa. It is known that if this barrier breaks down in humans the mother may become sensitized to certain blood group antigens of the foetus and that haemolytic disease of the foetus may result, and it seems quite likely that much unexplained foetal morbidity and mortality may also turn out to be due to maternal immunization resulting from placental leaks.

A more subtle question was propounded by Sir MacFarlane Burnet who asked why the immunologically reactive cells of an individual do not react against all the tissues which make up his body. The discovery that some diseases are in fact due to "auto-immunization" adds point to Burnet's

question. By way of answer Burnet, and his colleague Fenner, postulated that all the cells of an individual carry a series of self-markers which his immunologically active cells learn to recognize, and they predicted that if an organism at an early stage of its development received an injection of cells from another individual, then, when it grew up, it would permanently accept transplants from the cell donor. Burnet has since modified his hypothesis, but his prediction has been shown to be true. The "injection" of cells may be performed experimentally; in addition in cattle, and very occasionally in other species including man, cells may be transferred between twins *in utero*, and when this happens even non-identical twins will subsequently permanently accept transplants from each other. Individuals who carry permanently in their bodies cells derived from another individual are known as chimeras, and are said to display specific immunological tolerance towards the foreign cells.

The upshot of all this is that it is possible to distinguish by transplantation the cells of any individual from those of all others even of the same species, except only when the individuals concerned are (a) identical twins, (b) members of a strain of animals which has been maintained by brother x sister mating for so long that it is genetically virtually uniform, and (c) non-identical twins which happen to be chimeras.

There appears the exciting possibility that in producing chimeras we may learn how to introduce characters which are hereditarily transmissible, and so achieve even in mammals a sort of biological transmutation comparable to the transmutation of elements achieved by nuclear physics.

The surgical implications of the phenomena we have been considering are to me no less exciting, but this is another story and one which I must leave for another occasion.

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ANTI-EMETICS IN PREGNANCY AND TRAVEL SICKNESS

By R. F. RINTOUL

Based on a Dissertation read before the Royal
Medical Society on Friday, 20th November 1959.

The widespread use of anti-emetics is gradually increasing in this age of so-called social improvement and generalised travel. Their use is, however, more restricted than that of tranquillisers in the New World. Nowadays, we are much more drug conscious than half a century ago, but whether this is due to ourselves or to the ingenuity of our pharmacological experts in producing new drugs, it is hard to decide. There can be little doubt, however, that many factors in our modern existence are to be blamed, in some part at least, for the increased incidence of vomiting in pregnancy, and also of motion sickness as a whole. As yet, the precise aetiological factors in vomiting of pregnancy have not been elucidated, but it will be useful in discussing therapy to have a knowledge of how the two above-mentioned conditions are brought about.

Vomiting of Pregnancy

If vomiting itself has occurred since man's earliest existence, surely vomiting of pregnancy has occurred for even longer, but if we consider the current theories on its aetiology, it would appear that it is a product of civilisation and our method of existence. It is interesting to note that vomiting of pregnancy is unknown in the New Guinea islands. In other words, we can postulate that a socio-cultural factor is involved. Various theories have been suggested to account for vomiting of pregnancy. The *neurosis theory* is currently well favoured, but it seems that various other factors play a part in the production of vomiting. According to this theory, there is a rejection tendency on the part of the expectant mother, or a distorted attempt of the unconscious mind to get rid of the embryo—a tendency that is apparently quite compatible with a desire to have a child. The neurosis theory is substantiated by the fact that in many cases, treatment of the condition on psychological lines, or by mere admission to hospital has been successful. There can be little doubt that metabolic activity in the female is considerably altered during pregnancy, particularly during the early stages. It therefore seems reasonable to suppose that this could be due either to endocrine disturbances or to metabolic processes. During the early weeks of pregnancy, there are active changes in the endocrine system, and it has long been believed that in some way, a deficiency in the corpus luteum might produce vomiting. Extracts of the corpus luteum have, however, been given with indifferent results. Another suggested aspect of the *endocrine theory* has been that the excessive excretion of certain hormones during pregnancy is an indication of abnormal swelling of the anterior pituitary lobe, causing a sickness of cerebral origin. It has further been suggested that there is a temporary adrenal insufficiency, or that there is an allergic reaction from the endocrines, possibly due to the release of a substance from the implanted ovum. The previously well supported

theory of a toxin released from the placenta or foetus is no longer held. The system most affected by the metabolic changes of pregnancy is the carbohydrate system. The instability of liver glycogen metabolism leads to a deficiency when faced with hunger, and the demands of the growing foetus. The fast during the night leads to further depletion and consequently to mild ketosis, and nausea and vomiting result. The distaste for food often hinders replacement of the carbohydrate store, and this aggravates the ketosis. Morning sickness can, in this way, lead to the pernicious type, but a neurotic element is likely to be involved. The corrective measures which support this theory are a high carbohydrate intake, with free administration of fluids, and the injection of glucose if necessary. Mild sedation will produce helpful rest and quiet.

Typical vomiting of pregnancy is present in about 50% of all cases in the early months, and there are all grades to hyperemesis gravidarum. As soon as a patient suffering from morning sickness feels nausea, and vomits later in the day, she should be regarded as a mild case of hyperemesis, and treated accordingly. As in all good medicine, the first aim in treatment is to seek the cause of the disturbance and treat this condition. If, however, the precise aetiological factors involved are not easily recognisable, treatment is carried out on symptomatic lines. If necessary, fluid replacement or blood transfusion should be carried out, and also correction of electrolyte losses. Glucose infusions may also be helpful in vomiting of pregnancy. In the treatment of vomiting of pregnancy, adrenaline was first used about forty years ago as an anti-emetic, and its use has been reported again recently. It was believed to have a selective action on the cardiac and pyloric sphincters. No specific anti-emetic drugs may be singled out for use in vomiting of pregnancy. Of the antihistamine type, anthisan 100mg daily, and avomine 25mg daily, have been found equally effective, provided fluid loss is replaced and an adequate diet supplied. Due, however, to the vagueness in the aetiology of the condition, anti-emetics do not play a major therapeutic role in most cases.

Travel Sickness

Almost every normal individual is initially affected by motion sickness, but children below the age of two and the elderly are less susceptible. The literature which appeared on the subject prior to 1939 contained little factual information concerning this common disorder, but the one firm development had been the securing of evidence that the vestibular apparatus was essential in its production. Motion sickness is caused by frequent oscillatory movements of the body, and linear rather than angular acceleration is involved. Air sickness is due to linear acceleration in a vertical direction, i.e. a sudden rise or fall. This is similar in an elevator or a swing. The utricle of the otolith organ acts directly through the vomiting centre, causing the sequence of events leading to the act of vomiting. Sea-sickness also depends on the labyrinth, but is caused by the conflict of data. Visual information is normally the principal basis for orientation, data from the labyrinth and proprioceptive systems being interpreted in this light. Conflict therefore gives rise to an ill feeling, to dizziness and possibly headache. This is followed by sweating, and eventually nausea and vomiting occur. Susceptibility to sea-sickness can be reduced if the person is recumbent, and especially if the head is inclined backwards. In this position, the visual receptors and the utricular maculae in the labyrinth are removed from the plane of motion. The reason why infants do not suffer from motion sickness is that the labyrinth is as yet not functioning fully. A child who has suffered from infantile meningitis may have a functionless

labyrinthine and deaf mutes, as a rule, are not subject to motion sickness because in them the labyrinthine is underdeveloped. The cerebellum also plays a part in producing motion sickness, as removal of the flocculonodular lobe suppresses motion sickness without disturbing the vomiting reflex.

Attempts have been made to discover the physiological and psychological peculiarities of an individual which determine his degree of susceptibility to motion sickness. It appears that there is a dependency on a rather specific constitutional capacity of the individual to respond to certain patterns of vestibular stimulation, and that this can be modified to some extent by extralabyrinthine influences. 95% of susceptible persons have been found capable of adaptation without resort to the use of anti-emetics. Airmen include a persistently significant number of unfortunate individuals, both cadets and experienced flying personnel, who suffer from air-sickness when undergoing training or on joining a new unit. However, the number of these sufferers decreases considerably with each successive flight. With regard to susceptibility, a person may be resistant to one type of motion sickness, but not to another. Adaptation to a swing does not reduce air sickness, for example, and a person may be safe in a small boat, but very uncomfortable in a larger craft. The capacity to adapt to motion is minimal or entirely absent in these highly susceptible individuals, who constitute between three and five per cent of the population, and it is this group which must turn to the anti-emetics for comfort. Drugs given by mouth when the sickness has begun may not, however, be absorbed, and the administration should therefore be begun before the onset of nausea. The presence of food tends to stimulate the atonic inert stomach, and nausea may be decreased by this alone without the use of anti-emetics. Thus, when drugs are not available to serve as prophylaxis of motion sickness, the recommendation by sailors to nibble dry biscuits or bread at frequent intervals has much to be said for it.

The drugs used in the prevention of motion sickness can be divided into three groups. Drugs such as amphetamine, ephedrine and caffeine stimulate the brain, while barbiturates, bromides and chlorbutol depress the central nervous system during the control of motion sickness. The third group of drugs are those having a specific action in motion sickness, such as the belladonna alkaloids, atropine, l-hyoscyamine and hyoscine. Hyoscine hydrobromide was put to great use on service personnel during World War II. A dose of 0.6 mg. given one hour before rough water was encountered protected half the susceptible persons, and a double dose was required to help three-quarters. The equivalent dose of the other alkaloids is 1.0 mg. More recently, a new series of drugs has been used, of the antihistamine type; these act by depressing the overstimulated labyrinthine structure of the inner ear. Dramamine, a compound of diphenhydramine and a theophylline derivative, and avomine, a similar compound which has promethazine as its antihistamine moiety are both popular, but they produce the side effect of drowsiness, and should not be used by drivers and air pilots. Hyoscine is more specific as it does not produce drowsiness in the dose required to prevent sea sickness. Chlorpromazine, although a valuable therapeutic weapon for the relief of symptomatic vomiting, has no real place in the prevention of motion sickness, and the same is true of the recently introduced promazine and perphenazine. Many antihistamines have been used prophylactically in travel sickness, but due to the variability of their actions and side effects, the perfect solution has not yet been obtained.

Bright and Bright's Disease

BY E. A. W. SLATER

Based on a Dissertation read before the Royal Medical Society on Friday, 11th December 1959.

Richard Bright was born in 1789, the year in which George Washington became first President of the United States of America and France suffered a revolution. His father was a banker living in Bristol, an important city resting on the laurels of five centuries of maritime enterprise. The circumstances of his arrival were but the first of Bright's fortunes for he was a man on whom the sun consistently shone. He had the very best education, locally in Bristol and subsequently at the school of medicine in Edinburgh; he achieved early and continuous success in medicine and lived to enjoy its reflection; he travelled extensively; he had the largest general practice in London and the best facilities for clinical and pathological research; he was a copious author and a delicate artist; he retired young to enjoy his leisure and he died unobtrusively in his 70th year. During his lifetime he was associated with some of the greatest names in medicine; he became himself one of the greatest names in medicine.

As he is indubitably a giant figure in our medical history, I think it is worthwhile to examine his biography more minutely before going on to describe his contributions to medicine, and, more particularly, to renal disease.

I can find no evidence that Bright was anything special at school, which he attended in Bristol and Exeter. A portrait of him hitting his mother shows that he was a pretty, if aggressive, child. At any rate, he decided for medicine and arrived in Edinburgh in 1808 to enter the course. While he was here he became a member of the Royal Medical Society delivering two dissertations on "Gangrene" and "Retroversion of the Uterus." These were the first of his contributions to medical literature. In 1811, he continued his studies at Guy's Hospital, but two years later he was back in Edinburgh to graduate M.D. Bright then turned his back on his medical school for ever and, after some years of travel, returned to Guy's—at that time, as now, a Mecca of medicine. With his appointment as Assistant Physician in 1820, his feet were firmly on the great ladder to the top of which they were quick to set out.

From this time until his retirement in 1843, Bright served Guy's continuously. His was just one of the names on the hospital staff of that time which are familiar to us today. A senior member was Sir Astley Cooper, the most popular teacher of Anatomy and Surgery in London. Cooper encouraged and advised Bright prior to the publication of his first and greatest work, and the author accorded him lavish acknowledgement in the preface. But probably more famous still are the names of the two colleagues with whom Bright formed a great triumvirate—one of the finest in the history of any hospital and certainly in that of Guy's. Thomas Addison and Thomas Hodgkin have both left their names in our textbooks. Addison was Bright's close colleague and collaborator for over twenty years, and dominated the medical school for a quarter of a century. He was an eloquent lecturer, a great clinician, and a magnet for the students. But his

fame in his lifetime was local and he never achieved the universal recognition of Richard Bright. Hodgkin performed the autopsies on almost all Bright's cases and described himself "Hodgkin's Disease" which now perpetuates his name. It is easy to see that Guy's at this time claimed a formidable teaching team, and it is a happy reflection that the three greatest components graduated at the University of Edinburgh.

Before coming on to discuss Bright's great contribution to medical history, I must refer briefly to his interests outside medicine. He lived in days when a student with money and recreations had time to self-indulge and there is no doubt that the qualities of minute and accurate observation which he later brought to his medical writing, had been bred far from the hospital ward and post-mortem room. He was a biologist, a linguist, a traveller of enthusiasm and an author of some distinction. While at this University, he sailed to Iceland with Sir George Stewart MacKenzie, a noted geologist, and amassed botanical and zoological material for a contribution to MacKenzie's published account of the expedition. On his way home he was fortunate enough to be blown ashore on the Orkneys, from which islands, however, he quickly sailed for Leith. In 1814 he was abroad again, in Berlin, in Vienna during the famous Congress, and then travelling widely in Hungary. While in Vienna he had an audience of the King of Rome, an infant whom the doctor did not impress, and on his way home he stood on the field of Waterloo a fortnight after the defeat of the King of Rome's father, Napoleon Buonaparte. In London again, Bright published a graphic travelogue, which loses little by comparison with his subsequent medical literature.

I have now outlined the background to the life's work of Richard Bright. The man I have described was, in everything he did, a keen and thorough student, an accurate observer, a rigid recorder, above all an ardent enthusiast. To medicine he was a devotee: let us now see what medicine got from him.

The first published account of Bright's work appeared in 1827 in three volumes entitled "Reports of Medical Cases selected with a view of illustrating the Symptoms and Cure of Diseases by a reference to Morbid Anatomy." The first part of Volume 1 deals with diseases of the kidney and it is now a landmark in the history of medicine. Twenty-three cases are described which had been under his care, and, in all, the emphasis is on the association of albuminous urine with dropsical effusions or anasarca. Each case is followed to the post-mortem room, where, with the aid of Hodgkin, Bright consistently demonstrated structural derangement of the kidney visible to the naked eye. There are five delicately executed plates which cover a wide range of renal pathology.

In the preface to this volume, Bright gives an explanation of the significance of these cases. Dropsy, by which he meant effusions into the body cavities and tissues, was clinically evident in diseases of the heart, the liver or the kidneys, but only in the latter case—renal disease—was it associated with albumen in the urine. He began to feel that the association of dropsy and albuminous urine in any patient indicated kidney pathology, and the 23 cases he presented in this volume illustrate how his clinical suspicions were confirmed at autopsy. He also remarked that he had in almost all instances found some degree of hæmaturia.

The clinical and pathological details are very comprehensively presented, and in the course of his cases he describes perfectly the conditions we now know as Nephrosis and Chronic Nephritis. He suggests also that there are three possible morbid appearances of the kidney, and his descriptions coincide exactly with the contemporary nephrotic, chronic nephritic and

arteriosclerotic kidneys. It will be of value here to give two examples of the extraordinary precision with which Bright described conditions identical to those we come across today—130 years later.

John King, aged 34, had for three weeks had swollen limbs and oedematous hands and face. On admission he had scanty urine, about one pint in 24 hours. Shortly afterwards the urine became copious, dingy brown in colour and coagulable by heat. While in hospital he first of all suffered from Herpes Labialis, then Pneumonia and all the time from symptomatic treatment without hope. He eventually succumbed to pneumonia and was found at post-mortem to have considerable fluid in the pleura, pericardium, and abdominal cavity, a healthy liver, and kidneys—to quote Bright—“completely granulated throughout.”

Henry Izod, aged 25, suffered a slight attack of dropsy after which he was well for a year before he became swollen all over and died seven weeks later. His urine was not examined but after death his kidneys were found to be “almost white in external appearance, rather large and lobulated.” His heart was also slightly enlarged.

These two cases I have only outlined, Bright having given minute clinical and pathological detail. They serve, however, to demonstrate what an enormous alteration his observations must have made to contemporary thought on renal disease, and he experienced probably a unique credit when, with hardly a word of dissension, the medical world immediately began to talk about “Morbus Brightii”—Richard Bright’s disease—a title that selected itself for a condition which had not experienced material advance since the days of Rhophos in Greece, 1700 years before.

But Bright did not rest on his laurels. Several times in his publication of 1827 he had referred to an enlarged heart post-mortem—as, for example, in both the cases I have quoted above. In the Guy’s Hospital Reports of 1836, he refers to it again and also to a number of deaths from apoplexy in people suffering from renal disease. We now, of course, know how accurate his observations were for the subsequent development of techniques for measuring blood-pressure has led us to recognise hypertensive encephalopathy and left heart failure as common terminal events in Chronic Nephritis.

This article of 1836 also contains a classical description of Acute Nephritis. The frequency of Scarletina in the aetiology is pointed out and we are assured that “nice analysis of the blood will frequently detect a great deficiency of albumen, and sometimes manifest indications of the presence of urea.” We know very little more in 1960 about Types I and II Nephritis and Chronic Nephritis than was pointed out by Bright in these two papers. Only the arrival of the microscope and the sphygmomanometer have at all improved our knowledge without, regretably, a parallel advance in treatment.

Only one proposal of Bright’s do we challenge today and that is his effort to persuade us of the importance of drink in the aetiology of nephrosis. Looking back from our age of temperance, we label it coincidence that so many of his patients were also alcoholics and chronic dissipants.

In the Guy’s Hospital Reports of 1836, he further presented a tabular view of the morbid appearances of 100 cases who had died with albuminous urine. All were found to have either hard, contracted kidneys or large, soft kidneys, and the most frequent causes of death were cerebral derangements and intercurrent infections. Many were found to have hypertrophied hearts and oedematous lungs, but overall the other organs were healthy. These observations are all very basic in our present knowledge of the outcome of subacute and chronic Bright’s Disease.

His fourth publication on renal disease—the Gulstonian lecture of 1833—presented a summary of the signs he had come to associate with albuminous urine—anasarca, uræmia, absence of urea from the urine, infections, cardiac hypertrophy, cerebral symptoms and pathology of the kidneys.

Bright died in 1838 at the height of a widespread and just reputation. His contribution to all branches of clinical research had been prolific—the heart, the liver, the spleen, the pancreas, the Gastro-intestinal tract, and the Central Nervous System—all had been faithfully observed in their pathological behaviour in life and appearance after death. He was a cheerful and attractive personality always careful to acknowledge the assistance of his juniors. In his heyday he had had no competition in research into kidney disease: the scope and detail of his own findings hardly encouraged it. But at the time of his death he had been retired from Guy's for 15 years, and would-be competitors, having sat back to take stock of the whole new concept, had in the meantime set the ball rolling again. So nephritis left Bright behind and emerged into the present century, where the successive efforts of Volhard and Fahr, Dorothy Russell and Ellis to classify his disease have detracted nothing from, and added many complications to, the original simple account of Richard Bright himself.

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Consumer Research

At about the beginning of June, one in three of all Edinburgh medical students will receive a questionnaire from the Professor of Public Health and Social Medicine. The questions to be asked cover such topics as: factors which influenced the student's decision to enter medicine; his reactions to the medical school; his views on different phases of the medical curriculum and on medical education generally; his views on different branches of medical practice, and his own career plans.

This questionnaire represents the first stage of a national enquiry launched by the Association for the study of Medical Education. All medical schools are now engaged on a re-appraisal of their curricula and their teaching methods, and the Association for the Study of Medical Education (or ASME, as it is generally known) recognises that the value of these discussions is likely to be very greatly increased if they take full account of the medical student—his background, his interests and his reactions. Accordingly, all medical schools in Britain will be invited to participate in this enquiry, and the Edinburgh University Department of Public Health and Social Medicine is to carry it out on behalf of ASME.

If this information is to make a real contribution to current discussion, it must be collected and analysed within the next year. The main enquiry is scheduled to take place at the beginning of the Spring Term, 1961. Before then the results of the pilot study must have been studied in detail and the questionnaires modified to take account of any flaws which the pilot survey may show up and adapted to meet the special circumstances of the various participating medical schools. This explains why the first (pilot) questionnaire has to be launched at a time of the year which is by no means ideal from the point of view of the majority of students. It is hoped, however, that the students concerned will appreciate the reasons for the timing, and will find an opportunity to give a considered opinion in answer to questions which he is sure they will find interesting and relevant.

This is an important investigation, and one which should have a real and lasting influence on medical education in Britain. Edinburgh students, being in the forefront of the enquiry, have a special opportunity to increase its value and its impact.

Hospital Architecture in Britain

"The hospitals built now will represent our age to future generations. It is essential that they are not only functionally efficient but aesthetically desirable. The architecture about us affects our attitudes—both conscious and subconscious. Design is the concern of us all."

These were the beliefs presented to us by Mr Bruce Ritson and the Museum Committee when they brought an exhibition on contemporary hospital architecture to the Royal Medical Society in February. The material for the display, which was accumulated with care and effort from several sources, bespoke the concern for, and interest in, hospital design of the organisers. By showing us the best of what is new in Britain, they have equipped us to criticise and thus to play our part in the development of the hospital in this country.

The vitality of the doctor/architect liaison was well emphasised. As Geriatric and Casualty departments grow, tuberculosis sanatoria become redundant. The architect designing alone can hardly be expected to

sympathise with such trends, and the doctor designing alone cannot adequately cater for them. They must stand together, and, where luck runs low, fall together: by experiment and the pooling of experience, the best will be built into the hospitals of tomorrow, and they will appeal from both the functional and aesthetic points of view.

When this partnership is ill-balanced, design suffers and failure results: the completed building is unsatisfactory either to the architect or the doctor. Fortunately these failures are becoming rarer and were not represented among the plans, photographs and models on view in the Royal Medical Society. We were given here a complete idea of the good things that can emerge from a proper relationship between the doctor and the architect, and we were convinced that a knowledge of design is as important to the doctor as a knowledge of signs and symptoms.

This has been one of the most attractive features of a pleasant Session, and our thanks and congratulations go without reserve to the organisers, who have excelled themselves much to our benefit, and to the Department of Health for Scotland and the architects of the Western, Eastern and South-East Regional Hospital Boards who kindly lent the material for the exhibition.

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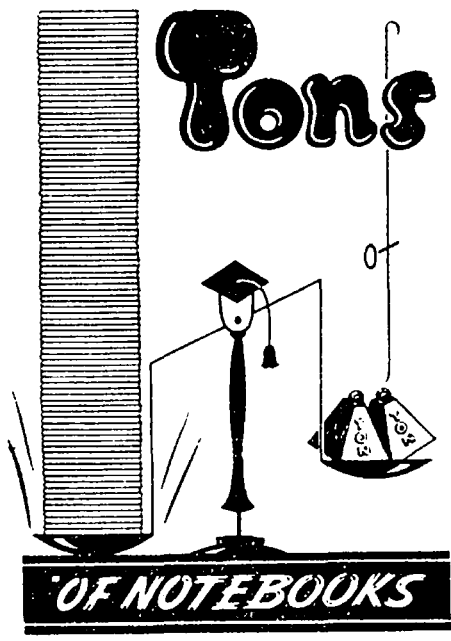
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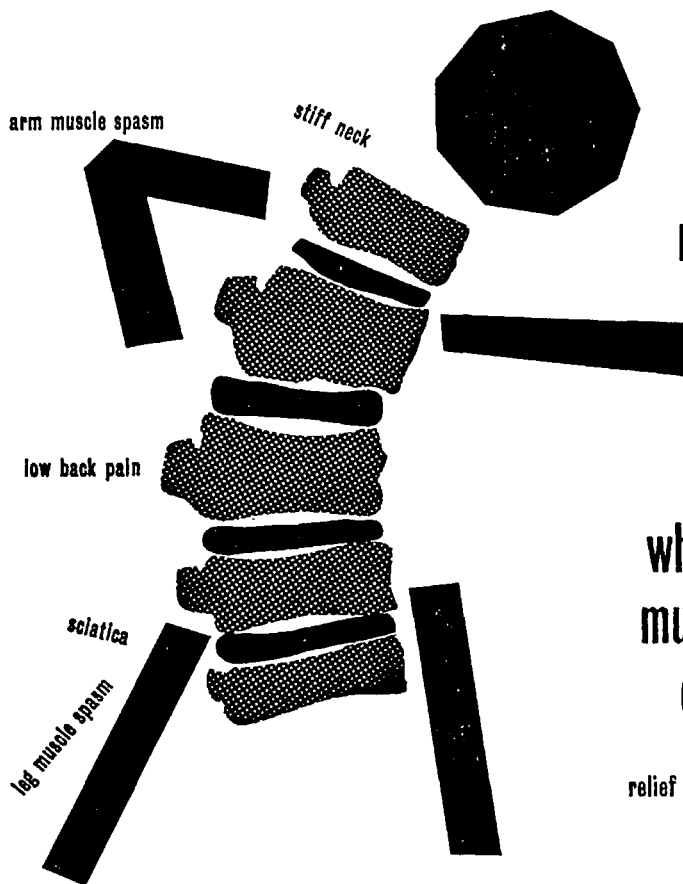
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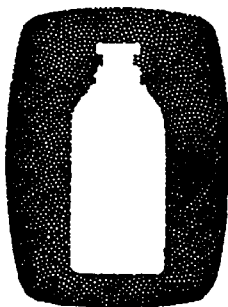
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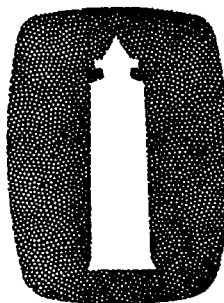
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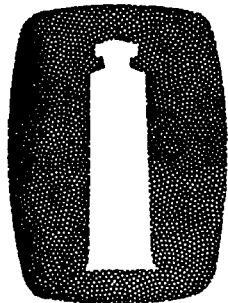
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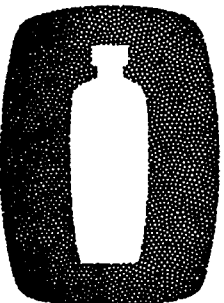
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